DRAFT
TOXICOLOGICAL PROFILE FOR
VINYL CHLORIDE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Vinyl Chloride was released in 1997. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road, NE
Mailstop F-32
Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
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Atlanta, Georgia 30333

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 7, 2003 (68 FR 63098). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999 (64 FR 56792) and October 25, 2001 (66 FR 54014) . Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Julie Louise Gerberding, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	**How Can (Chemical X) Affect Children?**
Section 1.7	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110 ***Fax:*** (770) 488-4178
E-mail: atsdric@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposure*s—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for vinyl chloride. The panel consisted of the following members:

1. Finis L. Cavender, Ph.D., Consultant in Toxicology, Henderson, North Carolina;

2. Sam Kacew, Ph.D., Professor, Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario; and

3. Andrew G. Salmon, Ph.D., Senior Toxicologist and Chief, Air Toxicology and Risk Assessment Unit, California Environmental Protection Agency, Lafayette, California.

These experts collectively have knowledge of vinyl chloride's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about vinyl chloride and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. EPA then places these sites on the National Priorities List (NPL) and targets them for federal long-term cleanup activities. Vinyl chloride has been found in at least 616 of the 1,647 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the number of sites at which vinyl chloride is found could increase as more sites are evaluated. This information is important because these sites may be sources of exposure, and exposure to this substance can harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you contact it—by breathing, eating, or drinking the substance or by skin contact.

Many factors will determine whether exposure to vinyl chloride will harm you. These factors include the dose (how much), the duration (how long), and the way you contact it. You also must consider any other chemicals to which you are exposed and your age, gender, diet, family traits, lifestyle, physiological status, nutritional status, and state of health.

1.1 WHAT IS VINYL CHLORIDE?

Vinyl chloride is known also as chloroethene, chloroethylene, ethylene monochloride, or monochloroethylene. At room temperature, it is a colorless gas, it burns easily, and it is not stable at high temperatures. Vinyl chloride exists in liquid form if kept under high pressure or at low temperatures. Vinyl chloride has a mild, sweet odor, which may become noticeable at 3,000 parts vinyl chloride per million parts (ppm) of air. However, the odor is of little value in preventing excess exposure. Most people begin to taste vinyl chloride in water at 3.4 ppm.

Vinyl chloride is a manufactured substance that does not occur naturally; however, it can be formed in the environment when other manufactured substances, such as trichloroethylene, trichloroethane, and tetrachloroethylene, are broken down by certain microorganisms. Production of vinyl chloride in the United States grew at an average rate of about 7% from the early 1980s to the early 1990s, with current growth at about 3% annually. Most of the vinyl chloride produced in the United States is used to make a polymer called polyvinyl chloride (PVC), which consists of long repeating units of vinyl chloride. PVC is used to make a variety of plastic products including pipes, wire and cable coatings, and packaging materials. Other uses include furniture and automobile upholstery, wall coverings, housewares, and automotive parts. At one time, vinyl chloride was used as a coolant, as a propellant in spray cans, and in some cosmetics. However, since the mid-1970s, vinyl chloride mostly has been used in the manufacture of PVC. Refer to Chapter 4 for more information about the chemical and physical properties of vinyl chloride. For more information about the production and use of vinyl chloride, see Chapter 5.

1.2 WHAT HAPPENS TO VINYL CHLORIDE WHEN IT ENTERS THE ENVIRONMENT?

Most of the vinyl chloride that enters the environment comes from vinyl chloride manufacturing or processing plants, which release it into the air or into waste water. EPA limits the amount that industries can release. Vinyl chloride also is a breakdown product of other synthetic chemicals. Vinyl chloride has entered the environment at hazardous waste sites as a result of improper disposal or leakage from storage containers or spills, but some may result from the breakdown of other chemicals. In addition, vinyl chloride has been found in tobacco smoke at very low levels.

Liquid vinyl chloride evaporates easily. Vinyl chloride in water or soil evaporates rapidly if it is near the surface. Vinyl chloride in the air breaks down in a few days, resulting in the formation of several other chemicals including hydrochloric acid, formaldehyde, and carbon dioxide.

Some vinyl chloride can dissolve in water. Vinyl chloride can migrate to groundwater and can be in groundwater due to the breakdown of other chemicals. Vinyl chloride is unlikely to build up in plants or animals that you might eat. For more information about what happens to vinyl chloride in the environment, see Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO VINYL CHLORIDE?

Because vinyl chloride usually exists in a gaseous state, you are most likely to be exposed to it by breathing it. Vinyl chloride is not normally found in urban, suburban, or rural air in amounts that are detectable by the usual methods of analysis. However, vinyl chloride has been found in the air near vinyl chloride manufacturing and processing plants, hazardous waste sites, and landfills. The amount of vinyl chloride in the air near these places ranges from trace amounts to over 1 ppm. Levels as high as 44 ppm were found in the air at some landfills. You can also be exposed to vinyl chloride in the air through tobacco smoke from cigarettes or cigars (both active smoking and second-hand smoke). Levels of vinyl chloride in tobacco smoke are very low, usually around 5–30 nanograms per cigarette (a nanogram is 0.000000001 gram).

You can be exposed to vinyl chloride by drinking water from contaminated wells. Most drinking water supplies do not contain vinyl chloride. In a 1982 survey, vinyl chloride was found in fewer than 1% of the 945 groundwater supplies tested in the United States. The concentrations in groundwater were up to 0.008 ppm. Other studies have reported vinyl chloride in groundwater at concentrations at or below 0.38 ppm. At one time, the flow of water through PVC pipes added very low amounts of vinyl chloride to water. For example, in one study of newly installed pipes, the drinking water had 0.001 ppm of vinyl chloride. No current information is available about the amount of vinyl chloride released from PVC pipes into water. In the past, vinyl chloride could get into food stored in materials containing PVC, but the U.S. government now regulates the amount of vinyl chloride in food packaging materials. When less than about 1 ppm of vinyl chloride is trapped in PVC packaging, vinyl chloride in detectable amounts does not enter food by contact with these products.

People who work at facilities that make vinyl chloride or PVC usually are exposed to higher levels than the general population. Work exposure occurs primarily from breathing air that contains vinyl chloride, but workers also are exposed when vinyl chloride contacts the skin or eyes. Based on studies using animals, it is possible that if vinyl chloride comes into contact with your skin or eyes, extremely small amounts could enter your body.

Please refer to Chapter 6 for more information on ways that people are exposed to vinyl chloride.

1.4 HOW CAN VINYL CHLORIDE ENTER AND LEAVE MY BODY?

If vinyl chloride gas contacts your skin, tiny amounts may pass through the skin and enter your body. Vinyl chloride is more likely to enter your body when you breathe air or drink water containing it. This could occur near certain factories or hazardous waste sites or in the workplace. At low levels (<20 ppm), most of the vinyl chloride that you breathe or swallow enters your blood rapidly, then travels throughout your body. When some portion of it reaches your liver, your liver changes it into several substances. Most of these new substances also travel in your blood; once they reach your kidneys, they leave your body in your urine. Most of the vinyl chloride is gone from your body a day after you breathe or swallow it. The liver, however, makes some new substances that do not leave your body as rapidly. A few of these new substances are more harmful than vinyl chloride because they react with chemicals inside your body and interfere with the way your body normally uses or responds to these chemicals. Some of these substances react in the liver and, depending on how much vinyl chloride you breathe in, may produce damage there. Your body needs more time to get rid of these changed chemicals, but eventually removes them as well. If you breathe or swallow more vinyl chloride than your liver can chemically change, you will breathe out excess vinyl chloride. Chapter 3 contains more information about how vinyl chloride enters and leaves your body.

1.5 HOW CAN VINYL CHLORIDE AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways to treat people who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing can help identify adverse health problems, such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal-care guidelines because laws today protect the welfare of research animals.

If you breathe high levels of vinyl chloride, you will feel dizzy or sleepy. These effects occur within 5 minutes if you are exposed to about 10,000 ppm of vinyl chloride. You can easily smell vinyl chloride at this concentration. It has a mild, sweet odor. If you breathe still higher levels (25,000 ppm), you may pass out. You can rapidly recover from these effects if you breathe fresh air. Some people get a headache when they breathe fresh air immediately after breathing very high levels of vinyl chloride. People who breathe extremely high levels of vinyl chloride can die. Studies in animals show that extremely high levels of vinyl chloride can damage the liver, lungs, and kidneys. These levels also can damage the heart and prevent blood clotting. The effects of ingesting vinyl chloride are unknown. If you spill liquid vinyl chloride on your skin, it will numb the skin and produce redness and blisters.

Some people who have breathed vinyl chloride for several years have changes in the structure of their livers. People are more likely to develop these changes if they breathe high levels of vinyl chloride. Some people who have worked with vinyl chloride have nerve damage, and others develop an immune reaction. The lowest levels that produce liver changes, nerve damage, and immune reaction in people are not known. Certain jobs related to PVC production expose workers to very high levels of vinyl chloride (i.e., pools of liquid vinyl chloride in vats or autoclaves). Some of these workers have problems with the blood flow in their hands. Their

fingers turn white and hurt when they go into the cold and may take a long time to recover when they go into a warm place. In some of these people, changes have appeared on the skin of their hands and forearms. Also, bones at the tips of their fingers have broken down. Studies suggest that some people may be more sensitive to these effects than others.

Some men who work with vinyl chloride have complained of a lack of sex drive. Studies in animals showed that long-term exposure can damage the sperm and testes. Some women who work with vinyl chloride have reported irregular menstrual periods. Some have developed high blood pressure during pregnancy. Studies of women who live near vinyl chloride manufacturing plants did not show that vinyl chloride produces birth defects. Studies using pregnant animals showed that breathing high levels of vinyl chloride (5,000 ppm) can harm unborn baby animals. Animal studies also show that vinyl chloride can produce more miscarriages early in pregnancy and decrease weight and delay skeletal development in fetuses. These same very high levels of vinyl chloride also caused harmful effects in the pregnant animals.

Results from several studies have suggested that breathing air or drinking water containing moderate levels (100 ppm) of vinyl chloride might increase their risk for cancer. However, the levels used in these studies were much higher than levels found in the ambient air and/or most drinking water supplies. Studies of workers who have breathed vinyl chloride over many years showed an increased risk for cancer of the liver. Brain cancer, lung cancer, and some cancers of the blood also may be connected with breathing vinyl chloride over long periods. Studies of long-term exposure in animals showed that cancer of the liver and mammary gland may increase at very low levels of vinyl chloride in the air (50 ppm). Lab animals fed low levels of vinyl chloride each day (2 mg/kg/day) during their lifetime had an increased risk of getting liver cancer.

The U.S. Department of Health and Human Services has determined that vinyl chloride is a known carcinogen. The International Agency for Research on Cancer has determined that vinyl chloride is carcinogenic to people, and EPA has determined that vinyl chloride is a human carcinogen.

More information about the adverse health effects of vinyl chloride in humans and animals can be found in Chapters 2 and 3.

1.6 HOW CAN VINYL CHLORIDE AFFECT CHILDREN?

This section discusses potential adverse health problems in people from exposures during conception to maturity (18 years of age).

No studies are available that specifically address the effects of vinyl chloride in children. The effects reported in exposed workers also could occur in children; however, the levels used in these studies were much higher than those found in ambient air and/or most drinking water supplies. Some studies suggest a possible association between birth defects and vinyl chloride exposure of the parents of affected children. Inhalation studies with animals have suggested that vinyl chloride might affect growth and development. Animal studies also suggest that infants and young children might be more susceptible than adults to vinyl chloride-induced cancer.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO VINYL CHLORIDE?

If your doctor finds that you (or a family member) have been exposed to substantial amounts of vinyl chloride, ask whether your children also might have been exposed. Your doctor might need to ask your state health department to investigate.

You can take some steps to limit your exposure to vinyl chloride. Very low levels of vinyl chloride exist in the ambient air, but these levels are usually not high enough to be a cause of concern. If you live near a hazardous waste site, municipal landfill, or a chemical plant that produces vinyl chloride or PVC, you might be exposed to higher levels of this compound than the general public. Vinyl chloride can leach from plastic PVC bottles or containers used to contain foods or beverages, but government agencies such as the Food and Drug Administration (FDA) have restricted the amount of vinyl chloride that can be present in these packages.

Tobacco smoke contains low levels of vinyl chloride, so limiting your family's exposure to cigarette or cigar smoke may help reduce their exposure to vinyl chloride.

People who work in facilities that manufacture or use vinyl chloride could be exposed to high levels of this chemical. The Occupational Safety and Health Administration (OSHA) regulates these levels and employers must comply with these rules. If you work in an industry that manufactures or uses vinyl chloride, strictly adhere to the rules provided by the safety officer and always use respirators when advised.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO VINYL CHLORIDE?

The results of several tests can sometimes show if you have been exposed to vinyl chloride, depending on the amount of your exposure and how recently it happened. However, scientists do not know whether these measurements can tell how much vinyl chloride you have been exposed to. These tests are not normally available at your doctor's office. Vinyl chloride can be measured in your breath, but the test must be done shortly after exposure. This test is not very helpful for measuring very low levels of the chemical. The amount of the major breakdown product of vinyl chloride, thiodiglycolic acid, in the urine may give some information about exposure. However, this test must be done shortly after exposure and does not reliably indicate the level of exposure. Also, exposure to other chemicals can produce the same breakdown products in your urine. Vinyl chloride can bind to genetic material in your body. The amount of this binding can be measured by sampling your blood and other tissues. This measurement will give information about whether you have been exposed to vinyl chloride, but it is not sensitive enough to determine the effects on the genetic material resulting from exposure. For more information, see Chapters 3 and 7.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. EPA, the Occupational Safety and Health Administration (OSHA), and FDA are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention (CDC) are two federal agencies that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels—in other words, levels of a toxic substance in air, water, soil, or food that do not exceed critical levels that are usually based on levels that affect animals; they are then adjusted to levels that will help protect people. Sometimes these not-to-exceed levels differ among federal agencies because the agencies used different exposure times (for example, an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are updated periodically as more information becomes available. For the most current information, check with the federal agency that provides it.

Vinyl chloride is regulated in drinking water, food, and air. Because it is a hazardous substance, regulations on its disposal, packaging, and other forms of handling also exist. EPA requires that the amount of vinyl chloride in drinking water not exceed 0.002 milligrams per liter (mg/L) of water (0.002 ppm). Under the EPA's Ambient Water Quality Criteria for the protection of human health, a concentration of zero has been recommended for vinyl chloride in ambient water.

To limit intake of vinyl chloride through foods to levels considered safe, FDA regulates the vinyl chloride content of various plastics. These include plastics that carry liquids and plastics that contact food. The limits for vinyl chloride content vary depending on the nature of the plastic and its use.

EPA has established a reportable quantity for vinyl chloride. If quantities greater than 1 pound (0.454 kilograms) are released to the environment, the National Response Center of the federal government must be told within 24 hours of the release.

OSHA regulates levels of vinyl chloride in the workplace. The maximum allowable amount of vinyl chloride in workroom air during an 8-hour workday in a 40-hour workweek is 1 ppm. The maximum amount allowed in any 15-minute period is 5 ppm. NIOSH recommends that the exposure limit (for a time-weighted average [TWA]) for vinyl chloride in air be the lowest reliably detectable concentration. Workers exposed to any measurable amount of it must wear special breathing equipment. EPA sets emission standards for vinyl chloride and PVC plants. The amount of vinyl chloride allowed to be emitted varies depending on the type of production and the discharge system used.

Further regulations and guidelines that apply to vinyl chloride are presented in Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR also can tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles also are available on-line at www.atsdr.cdc.gov and on CD-ROM. You can request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information

and technical assistance number at 1-888-42ATSDR (1-888-422-8737), by e-mailing atsdric@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

For-profit organizations may request copies of final Toxicological Profiles from

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO VINYL CHLORIDE IN THE UNITED STATES

Vinyl chloride is a one of the highest production volume chemicals in the world, with a current worldwide demand of roughly 16 billion pounds annually. Approximately 98% of all vinyl chloride produced is used to manufacture polyvinyl chloride (PVC). These PVC materials become end products in automotive parts, packaging products, pipes, construction materials, furniture, and a variety of other products. Other miscellaneous uses that account for about 2% of the vinyl chloride that is produced annually include the manufacture of 1,1,1-trichloroethane and copolymers with vinyl acetate, vinyl stearate, and vinylidene chloride.

Vinyl chloride's production and use results in its release to the environment in waste water streams and air emissions. The microbial degradation of trichloroethylene, tetrachloroethylene, and 1,1,1-trichloro-ethane also results in the formation of vinyl chloride. Most vinyl chloride released to the environment will eventually partition to air, where it is degraded by atmospheric oxidants such as hydroxyl radicals. The half-life for vinyl chloride in the atmosphere is about 1 day. In water and soil, vinyl chloride may slowly be degraded microbially or undergo hydrolysis, but the rate of these degradation reactions are slow in comparison to the rate of volatilization. Very low levels of vinyl chloride are usually present in ambient air with concentrations typically around 1 $\mu g/m^3$ (0.4 ppb) or less. In source dominated areas where vinyl chloride is being produced, higher levels are often observed. Elevated levels of vinyl chloride may also be found in the vicinity of hazardous waste sites and municipal landfills. For example, vinyl chloride was found in emissions from 85% of the landfills studied, and concentrations >2,600 $\mu g/m^3$ (1 ppm) were detected in more than half of the landfill emissions. Vinyl chloride possesses high mobility in soil, and as a consequence, is occasionally detected in groundwater and drinking water in the United States at levels in the parts per billion (ppb) range, although the rapid rate of volatilization generally attenuates the potential for vinyl chloride to leach substantially into groundwater.

The general population is primarily exposed to vinyl chloride from inhalation of ambient air and the ingestion of foods or other items that may contain low levels of vinyl chloride that has leached from a PVC container. Vinyl chloride possesses high mobility in the plastic and can leach into the food, beverages, or water that is ultimately ingested by the consumer. Dietary exposure to vinyl chloride from

PVC packages used for food has been calculated by several agencies and, based upon estimated average intakes in the United Kingdom and the United States, an exposure of <0.0004 µg/kg/day was estimated for the late 1970s and early 1980s. People who smoke may also be exposed to vinyl chloride since tobacco smoke has been shown to contain low levels of this compound. Much higher exposures are expected for persons that are employed in occupations where vinyl chloride is produced or used. Occupational exposure can arise from inhalation or dermal routes and may vary with specific job function (see Section 6.5).

2.2 SUMMARY OF HEALTH EFFECTS

The effects that have been reported to occur in humans in response to vinyl chloride exposure come almost exclusively from studies of workers exposed by inhalation in the workplace. Because women traditionally have not been employed in PVC-manufacturing positions in North America and Western Europe, most of the data on humans from these areas concerns effects in men. Also, virtually all of the epidemiological studies are limited by the absence of data on the actual levels to which workers were exposed. However, studies in animals by the inhalation and oral routes provide an indication of the doses of vinyl chloride that may be associated with similar effects.

Acute high-level exposure of humans to vinyl chloride (>8,000 ppm) is associated with the development of signs of intoxication such as dizziness, drowsiness, and/or headache. Reports from vinyl chloride workers and studies in animals indicate that loss of consciousness may also be associated with exposure to very high levels (>25,000 ppm). Two deaths connected with occupational exposure to vinyl chloride have been reported. Autopsy results from these men as well as autopsy results from animals dying from extremely high-level exposures indicate that levels of vinyl chloride producing death may produce lung and kidney irritation and inhibition of blood clotting. Cardiac arrhythmias have also been reported in animals as a result of acute exposure to very high levels of vinyl chloride (>100,000 ppm). At high concentrations (>30,000 ppm), vinyl chloride has been shown to sensitize the heart to epinephrine, resulting in cardiac arrhythmias in dogs. Cardiac sensitization by halogenated hydrocarbons generally occurs at very high air concentrations (0.5–90%). Therefore, it appears unlikely that persons exposed to low levels of vinyl chloride will experience these effects.

Longer-term exposure of humans in occupational settings has been associated with the development of a number of other toxic effects. However, exposure levels in these studies are generally not quantified, and thresholds for the effects have not been identified. Histopathological changes characteristic of vinyl

chloride exposure have been reported to take place in the liver. These changes include extensive fibrosis of the portal tracts and septa, and intralobular perisinusoidal regions, hepatocellular degeneration, sinusoidal dilation, and hypertrophy and hyperplasia of both hepatocytes and sinusoidal cells. These changes in liver structure in exposed workers develop in the absence of a measurable effect on liver function as determined by standard biochemical tests. Recent studies demonstrate morbidity and mortality related to fibrosis, portal hypertension, and cirrhosis among vinyl chloride workers. Reports indicate that peripheral neuropathy may also develop in some workers occupationally exposed to vinyl chloride. In addition, toxic effects on male reproductive function may occur. Studies in animals indicate that vinyl chloride may induce fetal resorptions, delayed development, and an increased incidence of the soft tissue anomaly, dilated ureter. When animals were exposed *in utero*, some changes in liver function were observed during adolescence. However, similar results have not been confirmed in humans.

A syndrome referred to as vinyl chloride disease has been observed in a small percentage of vinyl chloride workers, many of whom were employed as polymerization tank cleaners. This job exposed workers to high levels of vinyl chloride (>1,000 ppm). Vinyl chloride disease is very similar to systemic sclerosis and includes some or all of the following symptoms: Raynaud's phenomenon (fingers blanch and numbness and discomfort are experienced upon exposure to the cold), acroosteolysis (resorption of the terminal bones of the fingers and/or toes), joint and muscle pain, enhanced collagen deposition, decreased elasticity, and scleroderma-like skin changes. A few studies showed that Raynaud's phenomenon may gradually disappear upon removal from exposure. Bone resorption has continued after cessation of exposure in some cases, but not in all cases. Studies in animals support the findings observed in humans (i.e., blood vessel thickening, skin and skeletal changes). In addition, renal nephrosis has been reported to occur in animals exposed to vinyl chloride, but similar results have not been confirmed in humans.

Studies in both humans and animals indicate that vinyl chloride is carcinogenic. Hepatic angiosarcoma has been identified in workers exposed to vinyl chloride by the inhalation route. Other liver tumors, including hepatocellular carcinoma and cholangiocellular carcinoma, have also been associated with occupational exposure to vinyl chloride. Previous studies have also suggested that cancers of the central nervous system, and lymphatic and hematopoietic systems may occur in humans following occupational inhalation exposure. More recent studies, however, have not demonstrated an association between vinyl chloride exposure and brain, lung, or lymphatic/hematopoietic system cancers. Studies in a variety of animal species exposed by both the inhalation and oral routes show an increased incidence of hepatic

angiosarcoma. Therefore, it is appropriate to consider that vinyl chloride is carcinogenic by the oral route as well.

The National Toxicology Program of the Department of Health and Human Services has determined vinyl chloride to be a known human carcinogen. In addition, the International Agency for Research on Cancer (IARC) has concluded that sufficient evidence for carcinogenicity in humans and animals exists and has placed vinyl chloride in carcinogenicity category 1 (i.e., carcinogenic to humans). EPA also considers vinyl chloride to be a known human carcinogen. EPA's cancer risk assessment for vinyl chloride is discussed below in Section 2.3.

Death. Vinyl chloride, at sufficiently high levels, may be fatal to humans following inhalation exposure. The autopsy report regarding the deaths of two vinyl chloride workers showed congestion of the internal organs, particularly the kidneys and lungs, and failure of the blood to clot, but did not estimate the levels to which these workers had been exposed. Inhalation exposure of animals for as brief a period as 30 minutes to concentrations of vinyl chloride ranging from 100,000 to 400,000 ppm have been reported to be lethal to rats, mice, and guinea pigs. The cause of death was attributed to respiratory failure secondary to central nervous system depression in one study. However, reports of cardiac arrhythmicity in dogs at similar levels (>100,000 ppm) suggest that cardiac arrest may have contributed to the deaths. The levels of vinyl chloride found to cause death in animals are extremely high and are unlikely to exist under most environmental conditions (with the exception of concentrated emissions from a large point source). However, increased mortality was observed in pregnant mice when they were exposed to 500 ppm for 7 hours/day for 10 days during gestation. Therefore, it is possible that pregnancy might increase the susceptibility to the effects of vinyl chloride. Because of the limited solubility of vinyl chloride in water, acute ingestion of a lethal dose of vinyl chloride in contaminated water is improbable. Thus, it is unlikely that acute exposure to low levels of vinyl chloride in the air or water near hazardous waste sites will result in sudden death from cardiovascular effects.

No change in mortality rate was noted in a prospective cohort study of 1,100 workers exposed to vinyl chloride compared to the controls. Longer term, low-level exposures have been associated with decreased survival in a number of animal inhalation exposure studies and oral exposure studies. Decreased survival in the number of rats and mice was observed at inhalation exposures as low as 50 ppm for 6 hours/day, 5 days/week, for up to 10 months and oral exposures as low as 1.7 mg/kg/day over the course of a lifetime. The decreased survival rate noted in these studies may be a reflection of the increased mortality rate due to cancer induction by vinyl chloride.

The significance of a shortened lifespan in animals following low-level chronic exposure with regard to potential adverse effects in humans is unknown.

Hepatic Effects. Changes in the liver have been observed in humans exposed to vinyl chloride via inhalation. The characteristic pattern of changes consists of hypertrophy and hyperplasia of hepatocytes and sinusoidal cells; sinusoidal dilation associated with damage to the cells lining the sinusoids and/or sinusoidal occlusion associated with crowding due to cellular hypertrophy and hyperplasia; focal areas of hepatocellular degeneration due to disruption of hepatic circulation; and fibrosis of portal tracts, septa, and intralobular perisinusoidal regions. These findings are supported by studies in animals. The primary difference between effects observed in animals and humans was the greater degree of fibrosis (reticulin and collagen deposition) in human liver tissue. Structural changes occurred in the livers of humans and animals with little or no change in serum hepatic enzyme activities. The lack of change in serum biochemistry may have been due to the limited scope of the necrotic changes. Acute degenerative changes were seen in the livers of animals that inhaled extremely high levels of vinyl chloride. Areas of cellular alteration and necrosis were also observed in the livers of rats chronically exposed to vinyl chloride in the diet.

A recent IARC update of a multi-center cohort study demonstrated an increase in mortality from liver cirrhosis in workers exposed to moderate to high concentrations of vinyl chloride. The critical confounding factor of alcohol consumption was not considered in this study. Morbidity associated with liver cirrhosis was also reported to be elevated among vinyl chloride workers. Liver ultrasonography illustrated an increase in the incidence of periportal fibrosis in vinyl chloride workers. Portal fibrosis and portal hypertension were considered to contribute to mortality in several cases. Abnormal liver function was demonstrated in workers exposed to low concentrations of both vinyl chloride and ethylene dichloride.

Immunological and Lymphoreticular Effects. Increased levels of circulating immune complexes and immunoglobulins have been observed in vinyl chloride workers, indicating a stimulatory effect of vinyl chloride on the immune system. Increased percentages of lymphocytes have also been noted in exposed workers.

When workers with vinyl chloride disease were examined, a correlation between the severity of the symptoms of vinyl chloride disease (Raynaud's phenomenon, acroosteolysis, joint and muscle pain,

enhanced collagen deposition, stiffness of the hands, scleroderma-like skin changes) and the magnitude of the immune response was observed. The most frequent immunologic findings in workers with vinyl chloride disease were an increase in circulating immune complexes and cryoglobulinemia. As the severity of the clinical signs of vinyl chloride disease increased, there was an increase in B-cell proliferation, hyperimmunoglobulinemia, and complement activation.

Because of the similarity of vinyl chloride disease with the proposed autoimmune disease, systemic sclerosis, and the association of many autoimmune diseases with certain inherited genetic characteristics, the human lymphocyte antigen (HLA) phenotypes of vinyl chloride workers both with and without vinyl chloride disease were examined. The study authors determined that susceptibility to vinyl chloride disease was increased in the presence of the HLA-DR5 allele or a gene in linkage disequilibrium with it, and progression of the disease to its more severe forms was favored by HLA-DR3 and HLA-B8 phenotypes. Stimulation of the immune response has been observed in mice exposed to low-to-moderate levels of vinyl chloride via inhalation for several weeks.

Musculoskeletal Effects. Another characteristic of vinyl chloride disease is acroosteolysis, in which the terminal phalanges of the fingers are resorbed. Acroosteolysis in vinyl chloride workers was observed to be preceded by Raynaud's phenomenon in most instances. It is unclear whether the resorptive bone changes are due to activation of osteoclasts secondary to vascular insufficiency in the finger tips.

Cardiovascular Effects. A small percentage of workers exposed to vinyl chloride develop vinyl chloride disease. One of the symptoms of this disease is a condition referred to as Raynaud's phenomenon, in which the fingers blanch and feel numb and uncomfortable upon exposure to the cold. Arteriography and biopsy material from afflicted workers indicate that exposure to vinyl chloride may produce blockage of the blood vessels supplying the hand, hypervascularity, and a thickening of the blood vessel walls.

Vinyl chloride disease has been reported to be an autoimmune response similar to systemic sclerosis. Proposed mechanisms for the vascular effects elate the vascular response to the immunologic changes observed in these workers. According to these mechanisms, a reactive vinyl chloride intermediate metabolite, such as 2-chloroethylene oxide or 2-chloroacetaldehyde, binds to a protein such as IgG. The altered protein initiates an immune response, with deposition of immune products along the vascular endothelium. Circulating immune complexes are proposed to precipitate in response to exposure to the cold, and these precipitates are proposed to produce blockage of the small vessels.

Studies in rodents exposed by inhalation to high levels of vinyl chloride have reproduced these symptoms to some extent. Thickening of the arterial vessel walls has been observed in rats exposed to high concentrations of vinyl chloride (>5,000 ppm) for a year.

Limited data are available regarding cardiovascular-related deaths in humans; however, cardiac arrhythmias have been produced in dogs exposed by inhalation to extremely high levels of vinyl chloride (>100,000 ppm). It is unlikely that persons exposed to low levels of vinyl chloride in the air or water near hazardous waste sites will develop cardiac rhythm abnormalities due to vinyl chloride.

Neurological Effects. Central nervous system depression is the earliest symptom associated with acute high-level vinyl chloride exposure in humans and animals. Concentrations as low as 8,000 ppm may produce dizziness in humans exposed by inhalation. Workers exposed to vinyl chloride before occupational standards were made more rigorous, complained of dizziness, drowsiness, euphoria, nausea, headache, and occasional loss of consciousness. These symptoms were most frequently experienced by those employed in positions with the greatest exposure to vinyl chloride (cleaners of the autoclaves used to synthesize PVC).

A state of unconsciousness was produced in animals acutely exposed via inhalation to concentrations of approximately 100,000 ppm. It is unlikely that exposure to low levels of vinyl chloride in air or water near hazardous waste sites would produce central nervous system depression.

Reports suggest that peripheral nerve damage may occur in occupationally exposed workers. Chronic inhalation exposure of animals to high levels of vinyl chloride produce peripheral nerve damage and cerebellar degeneration.

Respiratory Effects. Both autopsy reports from workers with vinyl chloride-related deaths and animal studies with exposure to extremely high levels of vinyl chloride (100,000 ppm and above) indicate that such levels of vinyl chloride produce respiratory irritation.

Studies of workers who have been occupationally exposed to vinyl chloride give mixed results regarding the chronic adverse respiratory effects of vinyl chloride. Some studies reported no adverse respiratory effects associated with occupational vinyl chloride exposure. However, other investigators found increased incidences of emphysema, decreased respiratory volume and vital capacity, respiratory

insufficiency, decreased respiratory oxygen and carbon dioxide transfer, pulmonary fibrosis, and abnormal chest x-rays. Factors that may confound the interpretation of these results include a smoking history and exposure to PVC resin dust or to other chemicals.

Histopathologic examination of rats and mice exposed to vinyl chloride for periods of 6 months or a year provides some supportive evidence for the respiratory pathology associated with high-level exposure (2,500, 5,000, or 30,000 ppm). These studies identified changes such as proliferation and hypertrophy of the bronchiolar epithelium, hypersecretion of mucin, hyperplasia of the alveolar epithelium, mobilization of alveolar macrophages, increased pulmonary hemorrhages, and interstitial pneumonia.

Renal Effects. No evidence of human renal disease has been reported in studies of workers occupationally exposed to vinyl chloride. However, increased severity of tubular nephrosis and increased kidney-to-body-weight ratios were observed in rats exposed to concentrations of vinyl chloride ranging from 100 to 5,000 ppm for periods of up to a year. It is unclear whether the effects observed in rats represent an increase in severity of naturally occurring tubular nephrosis in rats, or whether these effects represent a lesion attributable to the toxic effects of vinyl chloride on the kidney.

Gastrointestinal Effects. Although adverse gastrointestinal effects such as gastritis and ulcers were reported in vinyl chloride workers, the significance of these effects is not known because no unexposed workers were used as controls. Other effects that have been reported, such as nausea, were found in workers who had been selected based upon liver dysfunction.

Hematological Effects. The blood of both humans and animals that died as a result of acute exposure to extremely high levels of vinyl chloride did not clot. Slight-to-severe thrombocytopenia has been observed in vinyl chloride workers in several, but not all, studies. However, studies in animals using nonlethal concentrations of vinyl chloride have indicated that such levels result in a decreased clotting time. In one study, a decrease was observed in the time necessary for blood to clot in rats exposed to 5,000 ppm for 1 year. However, the statistical significance of these effects was not reported. A decreased clotting time was observed in rats whose oral intake of vinyl chloride in the diet was 17 mg/kg/day for 2 years. Mean prothrombin time was significantly decreased after either 26 or 52 weeks. The contrast between the acute human studies and the chronic animal data suggest that the hematological effects of vinyl chloride are highly dose-dependent.

Endocrine Effects. One study of workers exposed to vinyl chloride found a thyroid insufficiency in most of those with scleroderma. Thyroid changes, including colloid goiter and increased perifollicular cells, were also noted in rats exposed to high levels of vinyl chloride for 1 year. In guinea pigs, no histopathological changes in the adrenal glands were reported after a 30-minute exposure to 400,000 ppm.

Dermal Effects. The third most common characteristic of vinyl chloride disease that was identified in persons with exposure to very high levels of vinyl chloride (such as polymerization tank cleaners) is thickening of the subepidermal layer of the skin. The changes in the skin may appear as thickening above the joints of the fingers or rope-like bundles on the hands and forearms. Analysis of biopsied tissue indicates that the thickening is due to increased synthesis and deposition of collagen. In most cases, the skin changes are also preceded by Raynaud's phenomenon. Thickening of the skin and increased collagen content have been reproduced to some extent in rats administered high concentrations of vinyl chloride by gavage.

Body Weight Effects. Workers who had been intoxicated by vinyl chloride were reported to have experienced anorexia, but no consistent changes in body weight were reported in rats exposed to up to 50,000 ppm for acute durations. No changes in body weight were reported in rats, mice, or rabbits exposed to 200 or 1,000 ppm vinyl chloride for up to 6 months. Body weight changes were noted in rats exposed to either 50 ppm vinyl chloride (10 months, 5 days/week, 5 hours/day) or 5,000 ppm vinyl chloride (4–52 weeks, 5 days/week, 7 hours/day). Maternal body weight gain was significantly decreased in mice exposed to 500 ppm for 7 hours/day during gestation days 6–15.

Reproductive Effects. Studies in humans indicate that the male reproductive function may be adversely affected by exposure to vinyl chloride. Decreased androgen levels have been found in workers occupationally exposed to vinyl chloride. Also, workers have complained of impotency and decreased libido. These findings are supported by histopathological evidence of testicular damage and decreased male fertility in rats exposed by inhalation.

Fewer studies have reported the effects of vinyl chloride on the reproductive function in females. Reduced hemoglobin levels during pregnancy and an increased incidence of elevated blood pressure and edema during pregnancy (preeclampsia) have been observed. Studies designed to examine these effects in animals were not located.

No adverse effects were noted in reproductive capability in a 2-generation study in rats exposed to vinyl chloride. Male and female Sprague-Dawley rats were exposed to 0, 10, 100, or 1,100 ppm vinyl chloride 6 hours/day for a 10-week premating period and a 3-week mating period. No exposure-related effects were seen in body weight, feed consumption, ability to reproduce, gestation index or length, or pre- and postweaning developmental landmarks. Sperm counts, motility, and morphology were also unaffected by vinyl chloride exposure.

Developmental Effects. Although a statistically significant increase in congenital abnormalities has been observed in members of some communities located near a vinyl chloride processing facility, reports have failed to establish a statistically significant association between developmental toxicity and either parental occupation or proximity to the facility. There are also inconsistencies in the developmental toxicity data for vinyl chloride in laboratory animals. In general, vinyl chloride produced minor developmental effects only at concentrations that were significantly toxic to maternal animals. Concentrations of 500 ppm for 7 hours/day were observed to produce delayed ossification in the fetus and decreased food consumption, body weight gain, and an increase in mortality rate in maternal mice. In contrast, no adverse effects were reported in an embryo-fetal developmental toxicity study conducted in rats exposed to vinyl chloride concentrations as high as 1,100 ppm for 6 hours/day. Embryo-fetal developmental parameters including uterine implantation, fetal gender distribution, fetal body weight, and fetal malformations and variations were not affected by vinyl chloride exposure. Vinyl chloride produced a decrease in maternal body weight gain; however, no changes were observed in feed consumption, clinical signs, or postmortem gross findings. Maternal liver and kidney weights were increased relative to body weight.

Cancer. A large number of studies have reported a greater than expected incidence of a rare type of cancer, angiosarcoma of the liver, among workers exposed to vinyl chloride. Other liver tumors, including hepatocellular carcinoma and cholangiocellular carcinoma, have also been associated with occupational exposure to vinyl chloride. Other types of cancer that have shown a statistically significant increase in incidence among vinyl chloride workers, in at least some studies, include cancer of the brain and central nervous system, the lung and respiratory tract, and the lymphatic/hematopoietic system. However, more recent studies have not confirmed an association between vinyl chloride exposure and brain, lung, or lymphatic/hematopoietic system cancers. A significant increase in cancers of connective and other soft tissues was observed in a recent follow-up mortality study and in a meta-analysis of eight independent studies. Rhomberg also suggests that vinyl chloride can induce soft tissue sarcoma outside of the liver; however, an IARC update of a multi-center cohort study was negative for soft tissue sarcoma.

A recent review pooled the analyses of worker cohort from 56 vinyl chloride plants in North America and Europe. This analysis includes over 22,000 workers and represents the most comprehensive data on occupational risks of vinyl chloride exposure. An elevated risk of liver cancer mortality was observed. Deaths from lung and laryngeal cancer were lower than expected and no excess cancer risk was observed for soft tissue sarcoma, brain, lymphoid, and hematopoietic system cancers. Lewis reports the continuing occurrence of angiosarcoma of the liver in retirees from a PVC production plant in Louisville, Kentucky. This ongoing incidence is reported primarily for those workers employed prior to 1960, suggesting that those exposed to the highest concentrations of vinyl chloride remain at risk for developing cancer for the remainder of their lives. The reported latency period for workers diagnosed prior to 1975 was 12–28 years, while those diagnosed after 1975 showed a latency of 27–47 years. Because women traditionally have not been employed in PVC-manufacturing positions in North America and Western Europe, virtually all of the information available from occupational studies in these areas is based on the responses of males to vinyl chloride. One study by Smulevich et al. reporting on Soviet males and females occupationally exposed to vinyl chloride indicates that females may have higher incidences of stomach cancer, leukemias, and lymphomas than males.

An increased incidence of angiosarcoma of the liver has been found after inhalation of vinyl chloride gas by a variety of animal species. Although no studies examining the incidence of carcinogenic effects in humans exposed to vinyl chloride by the oral route have been located, vinyl chloride incorporated into the diet of rats has been demonstrated to cause an increased incidence of hepatic angiosarcoma.

There are ample data on the genotoxicity of vinyl chloride in both humans and animals and information on the mechanisms by which this compound may exert its carcinogenic effects has been elucidated from both *in vitro* and *in vivo* studies (see Section 3.3).

Genotoxic Effects. Genotoxicity studies of vinyl chloride in humans include a large number of assays for chromosomal aberrations in the cultured lymphocytes of occupationally exposed workers. Workers exposed to vinyl chloride for an average of 15 years were shown to have elevated levels of micronuclei and chromosomal aberrations when compared to the unexposed controls. An increase in chromosome aberrations and micronuclei was correlated with exposure to vinyl chloride in the air at a plastics plant. Micronuclei counts were also significantly increased in a group of 52 workers exposed to vinyl chloride levels of 1.3–16.7 ppm compared to those of controls, but these increases were not observed in workers exposed to 0.3–7.3 ppm.

Increased sister chromatid exchanges have also been reported in occupationally exposed workers. Sister chromatid exchange frequencies were significantly increased compared to those of the controls at 0.003–7.3 ppm vinyl chloride. A positive correlation was reported between frequency of chromosomal aberrations and length and history of exposure. DNA single strand breaks present in human lymphocytes from exposed workers were quickly repaired following cessation of exposure. DNA damage in lymphocytes of plastic industry workers was also demonstrated by a single-cell gel electrophoresis technique. A correlation was observed between the severity of DNA damage and the duration of exposure. Induction of single-strand breaks in liver DNA was also observed in mice after inhalation of vinyl chloride. The reversibility of chromosome damage has been reported for several populations of workers following a cessation or reduction of exposure to vinyl chloride.

Vinyl chloride has also been demonstrated to be mutagenic in bacteria and yeast. Vinyl chloride is mutagenic in *Salmonella typhimurium*, but only in strains reverted by base-pair substitution by alkylating agents rather than by frameshift mutations. Metabolic activation is necessary for any mutagenic activity in this system or for a maximal response. In addition, vinyl chloride is mutagenic in the gaseous phase, but not when it is dissolved in water. The negative findings for vinyl chloride dissolved in water are most likely due to methodological problems associated with rapid evaporation and therefore do not reflect a lack of mutagenic potential. There is evidence that in *Salmonella typhimurium* and *Escherichia coli*, it is the oxidation of vinyl chloride to the reactive intermediates 2-chloroethylene oxide and 2-chloroacetaldehyde that is responsible for the mutagenicity of vinyl chloride.

Vinyl chloride is metabolized by mixed function oxidases (MFO) to form an epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranges to form 2-chloroacetaldehyde. Reactive metabolites of vinyl chloride can be transported intercellularly from parenchymal cells to the non-parenchymal cells. Many studies have characterized the mutation profile associated with DNA adducts formed by the reactive metabolites of vinyl chloride. Four primary DNA adducts are formed by the reactive metabolites of vinyl chloride. These are cyclic etheno-adducts that include, 1,N^6-ethenoadenine, 3,N^4-ethenocytosine, N^2,3-ethenoguanine, and 1,N^2-ethenoguanine. These adducts can produce base-pair (i.e., purine-to-purine or pyrimidine-to-pyrimidine exchange) transitions during transcription. DNA crosslinks can also be formed because chloracetaldehyde is bifunctional.

The role of etheno-adducts in the carcinogenesis of vinyl chloride has been recently reviewed. 2-Chloro-ethylene oxide and 2-chloroacetaldehyde can both react with DNA nucleotide bases; however, 2-chloro-

ethylene oxide is a more potent mutagen and may be the ultimate carcinogenic metabolite of vinyl chloride. Etheno-adducts generate mainly base pair substitution mutations. Mutations in specific genes (i.e., *ras oncogenes*, p53 tumor suppressor gene) have been identified in vinyl chloride-induce liver tumors in rats and humans and are discussed in further detail in Section 3.3.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

Studies in humans did not provide sufficient data regarding exposure levels and their correlation with observed effects. Therefore, animal studies were used for the derivation of inhalation MRLs.

- An MRL of 0.5 ppm has been derived for acute-duration inhalation exposure (≤14 days) to vinyl chloride.

This MRL was derived from a no-observed-adverse-effect level (NOAEL) of 50 ppm for developmental effects in mice exposed 7 hours/day on gestational days 6–15 (John et al. 1977, 1981). No adverse maternal or fetal effects were noted at 50 ppm, with the exception of an increase in crown-rump length that was not observed at 500 ppm. The 50-ppm exposure level is considered to represent a NOAEL for maternal and developmental toxicity. At the lowest-observed-adverse-effect level (LOAEL) of 500 ppm, delayed ossification was observed. An increase in resorptions at 500 ppm was considered to have been within historical control limits. There was frank maternal toxicity at 500 ppm (17% death). The NOAEL of 50 ppm for intermittent exposure (7 hours/day) was converted to a continuous exposure (50 ppm x 7/24 = 15 ppm).

Following EPA (1994g) methodology, the human equivalent concentration ($NOAEL_{HEC}$) for an extrarespiratory effect produced by a category 3 gas, such as vinyl chloride, is calculated by multiplying the duration-adjusted animal NOAEL by the ratio of the blood:gas partition coefficients in animals and humans $[(H_{b/g})_A / H_{b/g})_H]$. Since the partition coefficient in mice is greater than that in humans, as seen in Table 3-3, a default value of 1 is used for the ratio and the duration-adjusted animal NOAEL (15 ppm) is equivalent to the $NOAEL_{HEC}$ (15 ppm). A total uncertainty factor of 30 (3 for extrapolation from mice to humans using a dosimetric adjustment and 10 for human variability) was applied to the $NOAEL_{HEC}$.

Therefore, the acute-duration inhalation MRL = $NOAEL_{HEC}$ (15 ppm) ÷ 30 (UF) = 0.5 ppm.

- An MRL of 0.03 ppm has been derived for intermediate-duration inhalation exposure (15–364 days) to vinyl chloride.

An intermediate-duration inhalation MRL of 0.03 ppm was derived for vinyl chloride, based on a LEC_{10} value of 5 ppm for hepatic centrilobular hypertrophy in rats (Thornton et al. 2002). All dichotomous models in the Benchmark Dose Software (BMDS version 1.3.2) were fit to the incidence data for centrilobular hypertrophy in the rats exposed to vinyl chloride by inhalation (Thornton et al. 2002). The lower 95% confidence limit (LEC_{10}) of a 10% extra risk (LEC) for hepatic centrilobular hypertrophy was selected as the benchmark response for the point of departure. Several models provided equivalent goodness-of-fit statistics. Therefore, the LEC_{10} value of 3 ppm, derived from the simplest model (Weibull), was selected as the point of departure for calculating an intermediate-duration inhalation MRL (see Appendix A for more detailed information on the application of Benchmark Dose Modeling in deriving the intermediate-duration inhalation MRL for vinyl chloride). The LEC_{10} of 3 ppm was duration-adjusted from intermittent (6 hours/day) to continuous exposure (3 ppm x 6/24 = 0.8 ppm). Following EPA (1994g) methodology, the human equivalent concentration (LEC_{10HEC}) for an extrarespiratory effect produced by a category 3 gas, such as vinyl chloride, is calculated by multiplying the duration-adjusted animal LEC_{10} by the ratio of the blood:gas partition coefficients in animals and humans $[(H_{b/g})_A / H_{b/g})_H]$. Since the partition coefficient in mice is greater than that in humans, as seen in Table 3-3, a default value of 1 is used for the ratio and the duration-adjusted animal LEC_{10} (0.8 ppm)is equivalent to the LEC_{10HEC} (0.8 ppm). A total uncertainty factor of 30 (3 for extrapolation from mice to humans using a dosimetric adjustment and 10 for human variability) was applied to the $NOAEL_{HEC}$.

Therefore, the intermediate-duration inhalation MRL = LEC_{10HEC} (0.8 ppm) ÷ 30 (UF) = 0.03 ppm.

Increased relative liver weight (Bi et al. 1985; Sokal et al. 1980; Torkelson et al. 1961) and adverse histopathological changes (Lester et al. 1963; Schaffner 1978; Sokal et al. 1980; Wisniewska-Knypl et al. 1980) have been observed in several other intermediate-duration inhalation studies. Additional support for the selection of 10 ppm as the lowest LOAEL comes from another study demonstrating immunostimulation at 10 ppm (Sharma and Gehring 1979).

No chronic-duration inhalation MRL was derived for vinyl chloride because of the absence of a suitable LOAEL or NOAEL for derivation. A NOAEL (10 ppm) and a LOAEL (100 ppm) were identified for testicular effects (increases in the number of degenerative seminiferous tubule changes) in a chronic-duration inhalation study (Bi et al. 1985). However, these data were not used as the basis of a chronic-

duration inhalation MRL because the LOAEL for these effects was higher than the LOAEL of 10 ppm for nonneoplastic liver lesions identified in the intermediate-duration rat inhalation study of Thornton et al. (2002). Bi et al. (1985) did not report the incidence of histopathological changes in the liver following chronic inhalation exposure; however, the results of the Thornton et al. (2002) study suggest that liver effects would occur at lower doses than the reported testicular effects. No other chronic-duration inhalation toxicity studies were located in which vinyl chloride-induced nonneoplastic lesions were described.

Oral MRLs

Studies in humans did not provide sufficient data regarding exposure levels and their correlation with observed effects. Therefore, animal studies were used for the derivation of MRLs.

No acute- or intermediate-duration oral MRLs were derived for vinyl chloride because of an absence of data on the effects of oral exposure to vinyl chloride for these duration categories.

- An MRL of 0.003 mg/kg/day has been derived for chronic-duration oral exposure (≥365 days) to vinyl chloride.

This MRL of 0.003 mg/kg/day was based on a NOAEL of 0.17 mg/kg/day for noncancerous liver effects (i.e., liver cell polymorphism) in rats (Til et al. 1983, 1991) and application of the physiologically based pharmacokinetic (PBPK) model used to derive EPA's reference dose (RfD) (Clewell et al. 2001; EPA 2000). Source code and parameter values for running the rat and human models in Advance Continuous Simulation Language (ACSL) were transcribed from Appendix C of EPA (2000). Exposures in the Til et al. (1983, 1991) rat dietary study were simulated as 4-hour oral exposures with the NOAEL dose for liver effects of 0.17 mg/kg/day. A 4-hour feeding period was used in the study due to the rapid evaporative loss of vinyl chloride from the food. The total amount of vinyl chloride metabolized in 24 hours per liter of liver volume was the rat internal dose metric that was used in determining the human dose that would result in an equivalent human dose metric. One kilogram of liver was assumed to have an approximate volume of 1 L. Dose metrics reflect the cumulative amount of vinyl chloride metabolized over the 24-hour period. The human model was run iteratively, until the model converged with the internal dose estimate for the rat (3.16 mg/L liver). The human dose was assumed to be uniformly distributed over a 24-hour period with the resulting human equivalent dose of 0.09 mg/kg/day. Therefore, the human equivalent dose of 0.09 mg/kg/day, associated with the rat NOAEL of 0.17 mg/kg/day (Til et al. 1983, 1991), served as the basis for the chronic-duration oral MRL for vinyl chloride. A total uncertainty factor

of 30 (3 for extrapolating from animals to humans using a dose metric conversion and 10 for human variability) was applied to the human equivalent NOAEL.

Therefore, the chronic-duration oral MRL = 0.09 mg/kg/day (HED) ÷ 30 = 0.003 mg/kg/day.

More detailed information regarding the application of the PBPK modeling in deriving the chronic-duration oral MRL for vinyl chloride is provided in Appendix A.

EPA has concluded that sufficient evidence of carcinogenicity exists in humans and animals and has classified vinyl chloride according to its 1986 classification scheme as a Group A or known human carcinogen (EPA 1994c). EPA's current weight-of-evidence characterization for vinyl chloride concludes that vinyl chloride is a *known human carcinogen by the inhalation route of exposure*, based on human epidemiological data. By analogy, vinyl chloride is considered a *known human carcinogen by the oral route* because of positive animal bioassay data as well as pharmacokinetic data allowing dose extrapolation across routes. By inference, vinyl chloride is also considered highly *likely to be carcinogenic by the dermal route* because it acts systemically (EPA 2000). Because the epidemiological evidence does not provide sufficient exposure and incidence data to quantify risk based solely on human data, EPA cancer potency factors for inhalation and oral exposure have been calculated based on animal studies. An inhalation unit risk of 8.8×10^{-6} per ug/m^3 for continuous lifetime exposure from birth was estimated by EPA (2000) based on the incidence of liver tumors observed in rats in the inhalation study by Maltoni et al. (1981). An inhalation unit risk of 4.4×10^{-6} per ug/m^3 for continuous lifetime exposure during adulthood was also estimated by EPA (2000). An oral slope factor for continuous lifetime exposure from birth was estimated by EPA (2000) to be 1.5 per mg/kg/day based on the incidence of liver tumors in rats in the study by Feron et al. (1981). An oral slope factor of 7.5×10^{-1} per mg/kg/day for continuous lifetime exposure during adulthood was also estimated by EPA (2000).

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of vinyl chloride. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by adverse health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to produce significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between

"less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major adverse health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the adverse effects vary with dose and/or duration, and place into perspective the possible significance of these adverse effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of vinyl chloride are indicated in Tables 3-1 and 3-2 and Figures 3-1 and 3-2. Because cancer effects could occur at lower exposure levels, Figures 3-1 and 3-2 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for vinyl chloride. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised. It should be noted that MRLs are also

not protective in the case of altered health status caused by exposure to cigarette smoking or excessive alcohol consumption (i.e., altered lung and liver function).

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

A report by Danziger (1960) described the deaths of two vinyl chloride workers. In one case, a worker exposed to high concentrations of vinyl chloride emitted from an open valve was found dead. In another case, a worker responsible for cleaning a polymerization tank was found dead in the tank. Autopsies performed on these men showed congestion of the internal organs, particularly the lungs and kidneys, and failure of the blood to clot. Circumstances surrounding the deaths suggested that the deaths were due to breathing very high levels of vinyl chloride. No increase in mortality rate was noted in a prospective cohort study of 1,100 workers exposed to vinyl chloride compared to the controls (Laplanche et al. 1992). At the time of the study interview, 36% of the 1,100 workers were currently being exposed to vinyl chloride, and 64% had been exposed in the past (Laplanche et al. 1987, 1992).

Brief exposures to concentrations of vinyl chloride ranging from 100,000 to 400,000 ppm have been shown to be fatal in experimental animals such as rats (Lester et al. 1963; Mastromatteo et al. 1960), guinea pigs (Mastromatteo et al. 1960; Patty et al. 1930), and mice (Mastromatteo et al. 1960). At these concentrations, deaths occurred within 30–60 minutes. Male mice exposed to 30,000 ppm vinyl chloride 6 hours/day for 5 days, in a dominant lethal study showed an increased mortality rate (Anderson et al. 1976). An increased mortality rate was also observed at much lower concentrations in maternal mice in a developmental toxicity study (John et al. 1977, 1981). In this study, maternal mice had an increased incidence of deaths following exposure to 500 ppm for 10 days during gestation.

Decreased longevity was observed in intermediate-duration studies (Adkins et al. 1986; Drew et al. 1983; Feron et al. 1979a; Hong et al. 1981; Lee et al. 1978) and chronic-duration studies (Drew et al. 1983; Feron et al. 1979a; Viola 1970). A treatment-related increase in the mortality rate was observed in mice exposed to 500 ppm of vinyl chloride for 6 hours/day, 5 days/week, for 6 months (Adkins et al. 1986). In mice and rats maintained for 12 months following a 6-month, 6 hour/day, 5 day/week exposure regime,

decreased longevity was observed at concentrations as low as 50 ppm; however, statistical analyses of the data were not available to verify the significance of the decrease (Hong et al. 1981). Substantial increases in the mortality rate of mice and rats exposed to 250 ppm vinyl chloride for 12 months were observed by Lee et al. (1977a, 1978). In addition, small increases in mortality of mice and rats during the 12-month exposure period were observed at 50 ppm in these reports; however, quantitative data indicating the significance of these increases were not presented.

The influence of the age of female animals at the time of exposure to vinyl chloride on survival was examined by Drew et al. (1983). In female hamsters exposed to 200 ppm, two strains of female mice exposed to 50 ppm, and female rats exposed to 100 ppm for 12 months, a higher death rate was observed when 2-month-old animals were exposed than when 8- or 14-month-old animals were exposed. Similar trends were observed when hamsters and mice were exposed to these concentrations for 6 months. The treatment-related deaths in this study may be due to the induction of vinyl chloride-induced carcinogenesis. These results demonstrate the importance of the latency period for cancer and associated mortality. Animals that were exposed at a younger age had a longer post-exposure period for the development of tumors. It is difficult to assess the sensitivity of younger animals to cancer mortality in this study because the same exposure concentrations were used for each age group. These results do not necessarily indicate that young people are more susceptible to the lethal effects of vinyl chloride, since animals that were exposed later in life may have died of age-related causes prior to the expression of the lethal effects. This study was limited in that only one dose of vinyl chloride was tested in each species.

The highest NOAEL values and all reliable LOAEL values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for each study with a systemic end point in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Limited information is available on the acute adverse effects from inhalation of vinyl chloride by humans. Autopsy findings from a man who died after being overcome by vinyl chloride revealed the irritating nature of extremely high-level inhalation exposure. The lungs were found to be intensely hyperemic, and some desquamation of the alveolar epithelium had occurred (Danziger 1960).

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (NS)	30 min				300000 (5/5 died)	Mastromatteo et al. 1960
2	Mouse (CD-1)	5 d 6hr/d				30000 M (11/20 died)	Anderson et al. 1976
3	Mouse (CF-1)	10 d 7hr/d Gd6-15				500 F (17% maternal death)	John et al. 1977, 1981
4	Mouse (NS)	30 min				200000 (1/5 died)	Mastromatteo et al. 1960
5	Gn Pig (NS)	30 min				300000 (1/5 died)	Mastromatteo et al. 1960
6	Gn Pig (NS)	up to 8 hr				100000 (death)	Patty et al. 1930
	Systemic						
7	Rat (Holtzman)	1, 5 d 6hr/d	Hepatic	50000 M	100000 M (hepatocellular vacuolization, increased AKT and SDH)		Jaeger et al. 1974

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
8	Rat (NS)	30 min	Resp		100000	(lung hyperemia)	Mastromatteo et al. 1960
			Hepatic	100000	200000	(fatty infiltration changes)	
			Renal	200000	300000	(renal congestion)	
9	Rat (Holtzman)	1, 5 d 6hr/d	Hepatic	50000 M			Reynolds et al. 1975a
10	Rat (NS)	1 d 6hr/d	Hepatic	50000 M			Reynolds et al. 1975b
11	Rat (Sprague-Dawley)	4 hr/d Gd 6-19	Bd Wt	1100 F			Thornton et al. 2002

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
12	Mouse (NS)	30 min	Resp		100000	(lung hyperemia)	Mastromatteo et al. 1960
			Hepatic	200000	300000	(liver congestion)	
			Renal		100000	(degenerative tubular epithelium)	
13	Gn Pig (NS)	30 min	Resp		100000	(slight pulmonary hyperemia)	Mastromatteo et al. 1960
			Cardio	400000			
			Hepatic	200000	300000	(fatty degeneration)	
			Endocr	400000			
			Ocular	400000			
	Immuno/ Lymphoret						
14	Gn Pig (NS)	30 min		400000			Mastromatteo et al. 1960

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Neurological						
15	Human	3 d 2x/d 5min		4000	8000 (dizziness)		Lester et al. 1963
16	Rat (Fischer- 344)	1 hr		50000			Hehir et al. 1981
17	Rat (Fischer- 344)	2 wk 5d/wk 1hr/d		500			Hehir et al. 1981
18	Rat (Holtzman)	1, 5 d 6hr/d		50000 M		100000 M (anesthesia)	Jaeger et al. 1974
19	Rat (Sherman)	2 hr			50000 (moderate intoxication)		Lester et al. 1963
20	Rat (NS)	30 min				100000 (narcosis)	Mastromatteo et al. 1960

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form
21	Mouse (ICR)	1 hr		5000		50000	(ataxia)	Hehir et al. 1981
22	Mouse (NS)	30 min				100000	(narcosis)	Mastromatteo et al. 1960
23	Gn Pig (NS)	30 min				100000	(tremor, loss of consciousness)	Mastromatteo et al. 1960
24	Gn Pig (NS)	up to 8 hr		10000		25000	(narcosis)	Patty et al. 1930
	Reproductive							
25	Mouse (CD-1)	5 d 6hr/d		30000 M				Anderson et al. 1976
	Developmental							
26	Rat (Sprague-Dawley)	10 d 7hr/d Gd6-15			2500 F		(ureter dilation)	John et al. 1977, 1981

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
27	Rat (Sprague-Dawley)	4 hr/d Gd 6-19		1100			Thornton et al. 2002
28	Mouse (CF-1)	10 d 7hr/d Gd6-15		50 F[b]	500 F (delayed ossification)		John et al. 1977, 1981
29	Rabbit (New Zealand)	13 d 7hr/d Gd6-18			500 F (delayed ossification)		John et al. 1977, 1981
	Cancer						
30	Mouse (ICR)	1 hr				5000 (CEL: bronchioalveolar adenoma)	Hehir et al. 1981
	INTERMEDIATE EXPOSURE						
	Death						
31	Rat (CD)	1-10mo 5d/wk 6hr/d				50 (17/26 died)	Hong et al. 1981
32	Mouse (A/J)	6 mo 5d/wk 6hr/d				500 M (37/70 died) 500 F (23/70 died)	Adkins et al. 1986

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
33	Mouse (CD-1)	1-6 mo 5d/wk 6hr/d				50 (15/16 died)	Hong et al. 1981
	Systemic						
34	Rat (Wistar)	3 mo 6d/wk 6hr/d	Cardio	10 M	100 M (increased relative heart weight)		Bi et al. 1985
			Renal	100 M	3000 M (increased relative kidney weight)		
35	Rat (Wistar)	6 mo 6d/wk 6hr/d	Cardio		10 M (increased relative heart weight)		Bi et al. 1985
			Hepatic		10 M (increased relative liver weight)		
36	Rat (Sherman)	19 d 8hr/d	Hemato		50000 (decreased white blood cells)		Lester et al. 1963
			Hepatic		50000 (hepatocellular hypertrophy, large irregular vacuoles, compression of sinusoids, elevated relative liver weight)		
			Renal	50000			
			Dermal	50000 F	50000 M (thin coats, scaly tails)		

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
37	Rat (Sherman)	92 d 5d/wk 8hr/d	Hemato		20000 (decreased white blood cells)		Lester et al. 1963
			Hepatic		20000 (moderate hepatocellular hypertrophy, fine to medium vacuoles, compression of sinusoids)		
			Renal	20000			
38	Rat (Wistar)	10 mo 5d/wk 5hr/d	Musc/skel	20000 M			Sokal et al. 1980
			Hepatic		50 M (fatty changes)		
			Renal	50 M	500 M (increased kidney weight)		
			Bd Wt		50 M (10% decrease in body weight)		
39	Rat (Sprague-Dawley)	16 wk (M) 19 wk (F) 2 gen 6 hr/d	Hepatic		10[c] F (centrilobular hypertrophy in F1 female rats)		Thornton et al. 2002
			Bd Wt	1100			

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
40	Rat (NS)	6 mo 5d/wk 0.5-7hr/d	Hemato	200			Torkelson et al. 1961
			Hepatic		100 (increased relative liver weight)		
			Renal	200			
			Bd Wt	200			
41	Rat (Wistar)	10 mo 5d/wk 5hr/d	Hepatic		50 M (fatty changes)		Wisniewska- Knypl et al. 1980
42	Mouse (NS)	1-6 mo 5 d/wk 5 hr/d	Hepatic		2500 M (hyperplasia of hepatocytes and activated sinusoidal cells)		Schaffner 1978

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL: Less Serious (ppm)	LOAEL: Serious (ppm)	Reference Chemical Form
43	Mouse (CD-1)	8 wk 5 d/wk 6 hr/d	Hemato	1000 M			Sharma and Gehring 1979
			Hepatic		1000 M (decreased liver weight)		
			Renal	1000 M			
			Bd Wt	1000 M			
44	Mouse (CD-1)	5-6 mo 5 d/wk 5 hr/d	Resp		2500 M (proliferation and hypertrophy of bronchial epithelium; hypersecretion of mucin; hyperplasia of alveolar epithelium)		Suzuki 1978,1981
45	Rabbit (NS)	6 mo 5d/wk 7hr/d	Hepatic	100		200 (centrilobular degeneration and necrosis)	Torkelson et al. 1961
			Renal	200			
			Bd Wt	200			

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Immuno/ Lymphoret						
46	Rat (Wistar)	3 mo 6d/wk 6hr/d		100 M	3000 M (increased spleen weight)		Bi et al. 1985
47	Rat (Wistar)	6 mo 6d/wk 6hr/d			10 M (increased spleen weight)		Bi et al. 1985
48	Rat (Wistar)	10 mo 5d/wk 5hr/d			50 M (increased spleen weight)		Sokal et al. 1980
49	Mouse (CD-1)	2-8 wk 5 d/wk 6 hr/d			10 M (increased spontaneous lymphocyte proliferation)		Sharma and Gehring 1979
	Neurological						
50	Rat (Fischer- 344)	20wk 5d/wk 1hr/d		50			Hehir et al. 1981
	Reproductive						
51	Rat (Wistar)	3,6 mo 6d/wk 6hr/d		10 M	100 M (decreased testes weight)		Bi et al. 1985
52	Rat (CD)	11 wk 5 d/wk 6 hr/d		50 M		250 M (reduced male fertility)	Short et al. 1977

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
53	Rat (Wistar)	10 mo 5d/wk 5hr/d		50 M		500 M (spermatogenic epithelial necrosis)	Sokal et al. 1980
54	Rat (Sprague-Dawley)	16 wk (M) 19 wk (F) 2 gen 4 hr/d		1100			Thornton et al. 2002
	Cancer						
55	Rat (Fischer- 344)	6 mo 5 d/wk 6 hr/d				100 F (CEL: hepatic hemangiosarcoma, hepatocellular carcinoma, neoplastic nodules; mammary fibroadenoma)	Drew et al. 1983
56	Rat (Sprague-Dawley)	33 d 6 d/wk 8 hr/d				500 M (CEL: hepatocellular carcinoma, angiosarcoma of the liver, benign cholangioma, nephroblastoma, angiomyoma, leukemia, Zymbal gland carcinoma, pituitary adenoma, mammary carcinoma and fibroma.	Froment et al. 1994

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
57	Rat (CD)	6 or 10 mo 5d/wk 6hr/d				250 (CEL: liver hemangiosarcoma, neoplastic nodules)	Hong et al. 1981
58	Rat (Sprague-Dawley)	16 wk (M) 19 wk (F) 2 gen 4 hr/d				1100 F (CEL: foci of hepatocellular alterations considered to be pre-neoplastic)	Thornton et al. 2002
59	Mouse (A/J)	6 mo 5d/wk 6hr/d				50 (CEL: pulmonary adenoma)	Adkins et al. 1986
60	Mouse (CD-1)	6 mo 5 d/wk 6 hr/d				50 F (CEL: hemangiosarcoma of skin, peritoneum; mammary gland carcinoma; lung carcinoma)	Drew et al. 1983
61	Mouse (B6C3F1)	6 mo 5 d/wk 6 hr/d				50 F (CEL: hemangiosarcoma of subcutis, peritoneum; mammary gland carcinoma)	Drew et al. 1983

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
62	Mouse (CD-1)	1,3,6 mo 5d/wk 6hr/d				50 F (CEL: mammary gland adenocarcinoma/carcinoma)	Hong et al. 1981
63	Mouse (Swiss)	30 wk 5 d/wk 4 hr/d				50 (CEL: liver angiosarcoma and angioma)	Maltoni et al. 1981
64	Mouse (CD-1)	4 wk 5d/wk 6hr/d				100 M (CEL: lung alveogenic tumors)	Suzuki 1983
65	Hamster (Golden Syrian)	6 mo 5 d/wk 6 hr/d				200 F (CEL: liver hemangiosarcoma; skin hemangiosarcoma, spleen hemangiosarcoma; mammary gland carcinoma)	Drew et al. 1983
66	Hamster (Golden Syrian)	30 wk 5 d/wk 4 hr/d				500 M (CEL: liver angiosarcoma)	Maltoni et al. 1981

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Systemic						
67	Rat (Wistar)	12 mo 6d/wk 6hr/d	Hepatic	100 M	3000 M (increased liver weight)		Bi et al. 1985
			Renal	10 M	100 M (increased kidney weight)		
			Bd Wt	10 M	100 M (14% decrease in body weight)		
	Reproductive						
68	Rat (Wistar)	12 mo 6d/wk 6hr/d		10 M	100 M (degenerative seminiferous tubule changes)		Bi et al. 1985
	Cancer						
69	Rat (Wistar)	12 mo 6d/wk 6hr/d				100 M (CEL: liver angiosarcoma; lung angiosarcoma)	Bi et al. 1985
70	Rat (Fischer- 344)	12, 18, 24 mo 5 d/wk 6 hr/d				100 F (CEL: hepatic hemangiosarcoma, hepatocellular carcinoma, neoplastic nodules; mammary gland fibroadenoma and adenocarcino	Drew et al. 1983

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
71	Rat (CD)	1-12 mo 5 d/wk 6 hr/d				250 F (CEL: hepatic hemangiosarcoma)	Lee et al. 1978
72	Rat (Sprague-Dawley)	52 wk 5 d/wk 4 hr/d				5 F (CEL: mammary gland carcinoma)	Maltoni et al. 1981
73	Mouse (Swiss CD-1)	12, 18 mo 5 d/wk 6 hr/d				50 F (CEL: lung; hemangiosarcoma of peritoneum, subcutis; mammary gland carcinoma)	Drew et al. 1983
74	Mouse (B6C3F1)	12 mo 5 d/wk 6 hr/d				50 F (CEL: hemangiosarcoma of peritoneum, subcutis; mammary gland carcinoma)	Drew et al. 1983
75	Mouse (CD-1)	1-12 mo 5 d/wk 6 hr/d				50 F (CEL: mammary gland adenoma and adenocarcinoma)	Lee et al. 1977a, Lee et al. 1978
						50 (CEL: hepatic hemangiosarcoma; bronchiolo-alveolar adenoma; malignant lymphoma)	

Table 3-1 Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
76	Hamster (Golden Syrian)	12, 18, 24 mo 5 d/wk 6 hr/d				200 F (CEL: liver hemangiosarcoma; skin carcinoma, hemangiosarcoma; spleen hemangiosarcoma; mammary gland carcinoma; stomach a	Drew et al. 1983

a Numbers correspond to entries in Figure 3-1.

b Used to derive an acute-duration inhalation Minimal Risk Level (MRL) of 0.5 ppm. A NOAEL was adjusted for intermittent exposure and converted to a Human Equivalent Concentration (HEC) before applying uncertainty factors. The MRL was obtained by dividing the NOAEL-HEC by an uncertainty factor of 30 (3 for extrapolation from animals to humans using a dosimetric adjustment, and 10 for human variability).

c Used to derive an intermediate-duration inhalation MRL of 0.03 ppm. LEC10 converted to an HEC and adjusted for intermittent exposure before applying uncertainty factors. The MRL was obtained by dividing the LEC10-HEC by an uncertainty factor of 30 (3 for extrapolation from animals to humans using a dosimetric adjustment, and 10 for human variability).

AKT = alpha-ketoglutarate transaminase; B - both; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); derm = dermal; Endocr = endocrine; F = Female; Gd = gestational day; Gn pig = guinea pig; hemato = hematological; hr = hour(s); Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; SDH = sorbitol dehydrogenase; wk = week(s); x = time(s)

Figure 3-1. Levels of Significant Exposure to Vinyl Chloride- Inhalation

Acute (≤14 days)

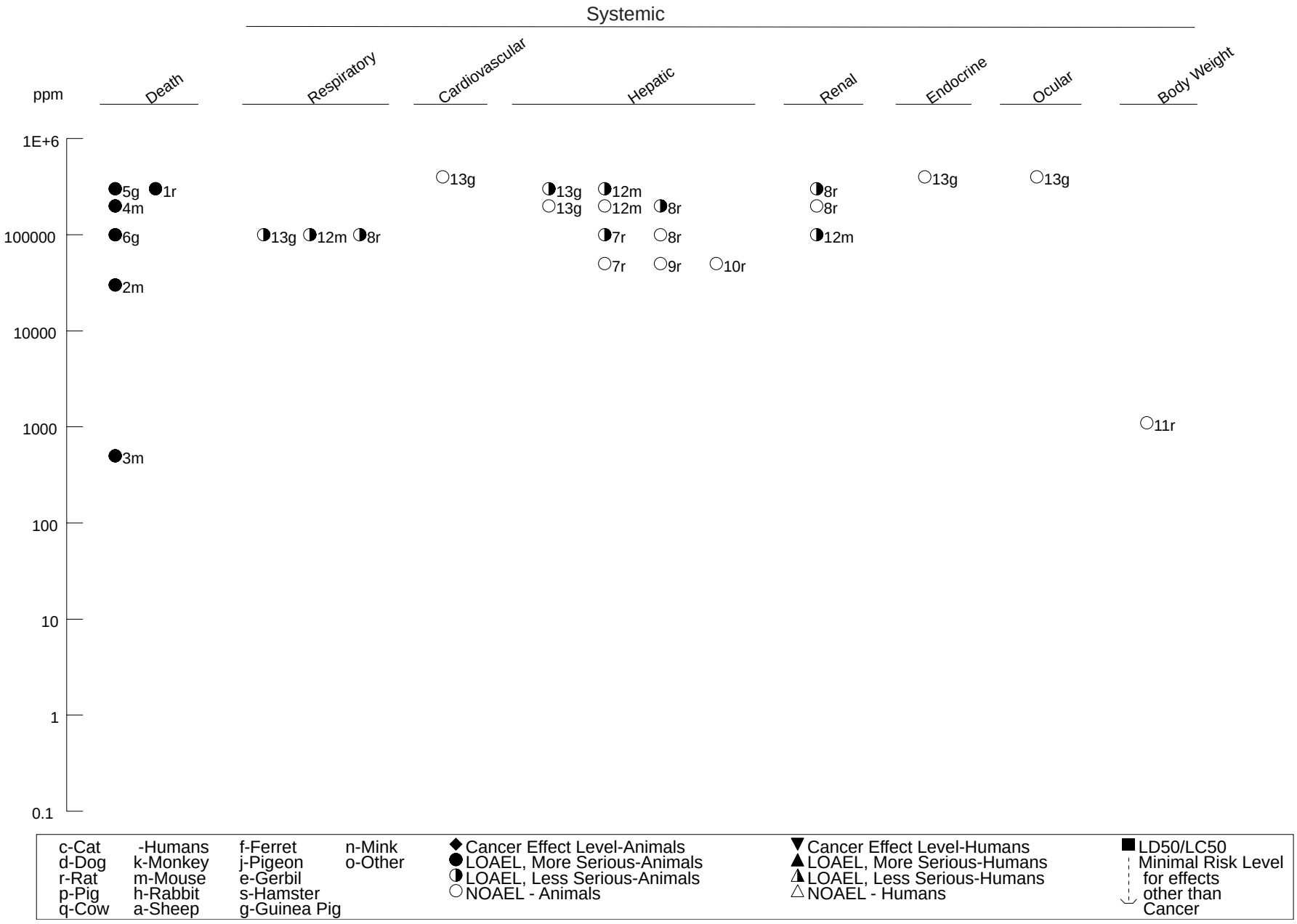


Figure 3-1. Levels of Significant Exposure to Vinyl Chloride- Inhalation (*Continued*)

Acute (≤14 days)

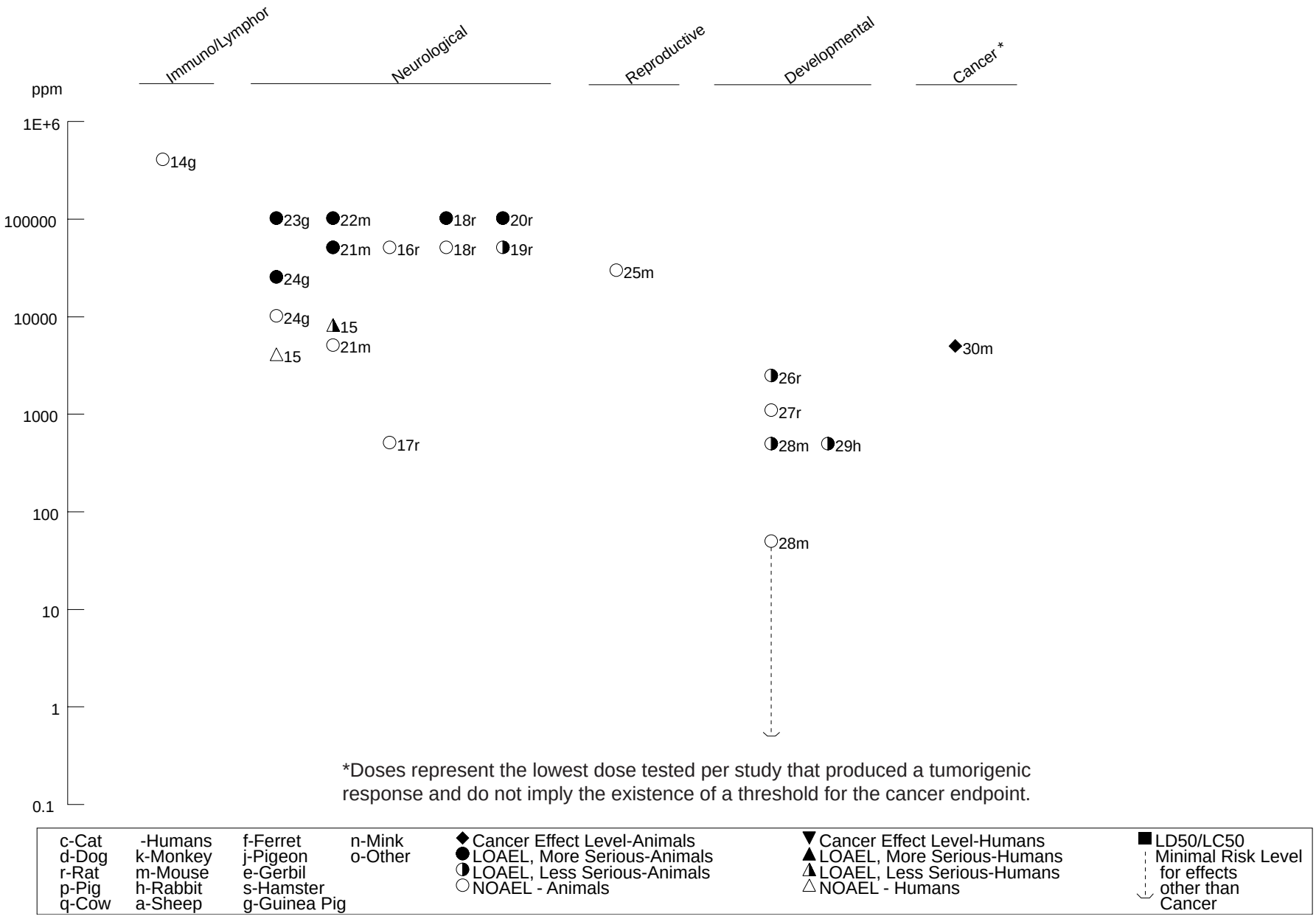


Figure 3-1. Levels of Significant Exposure to Vinyl Chloride- Inhalation (*Continued*)

Intermediate (15-364 days)

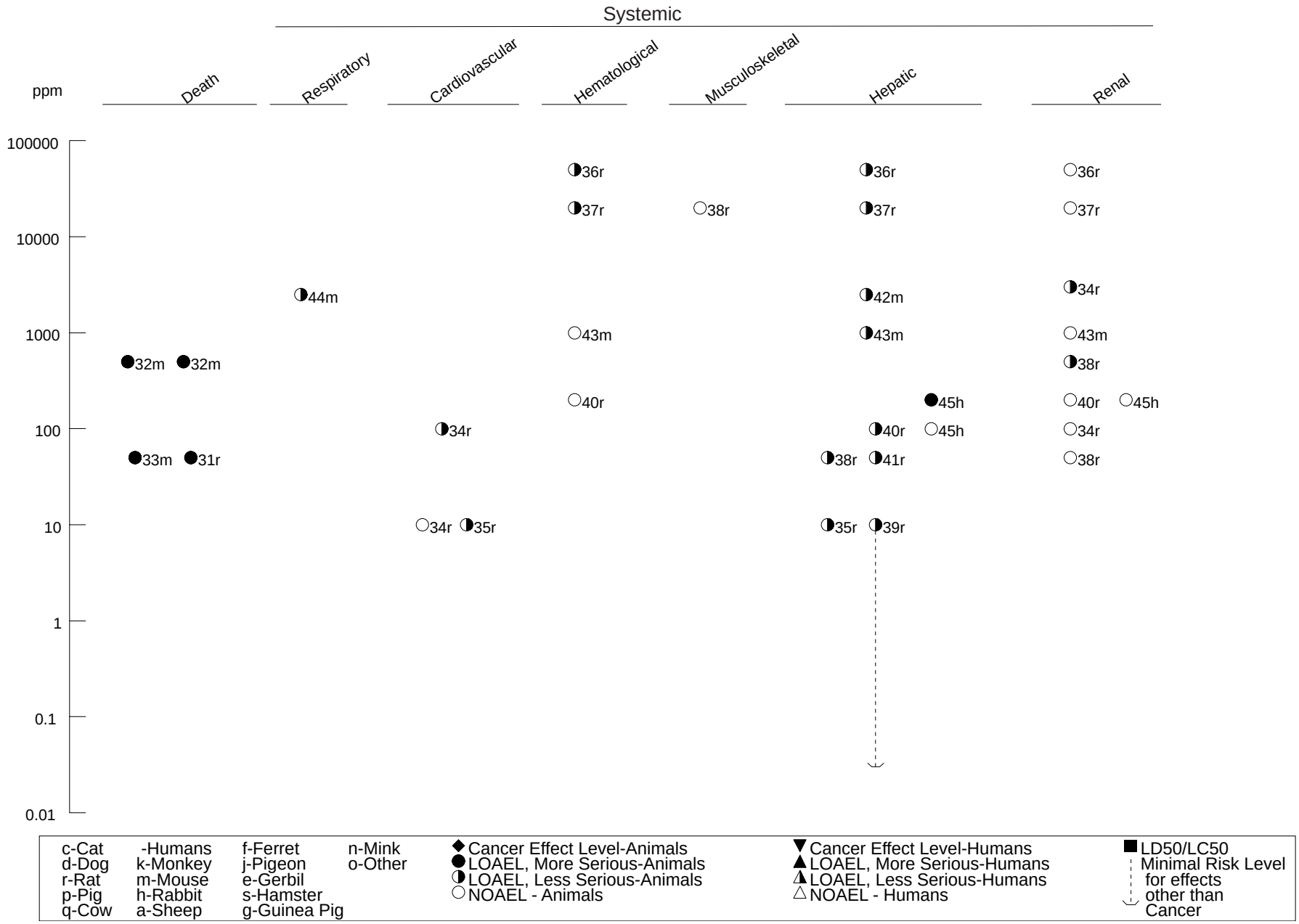


Figure 3-1. Levels of Significant Exposure to Vinyl Chloride- Inhalation (*Continued*)

Intermediate (15-364 days)

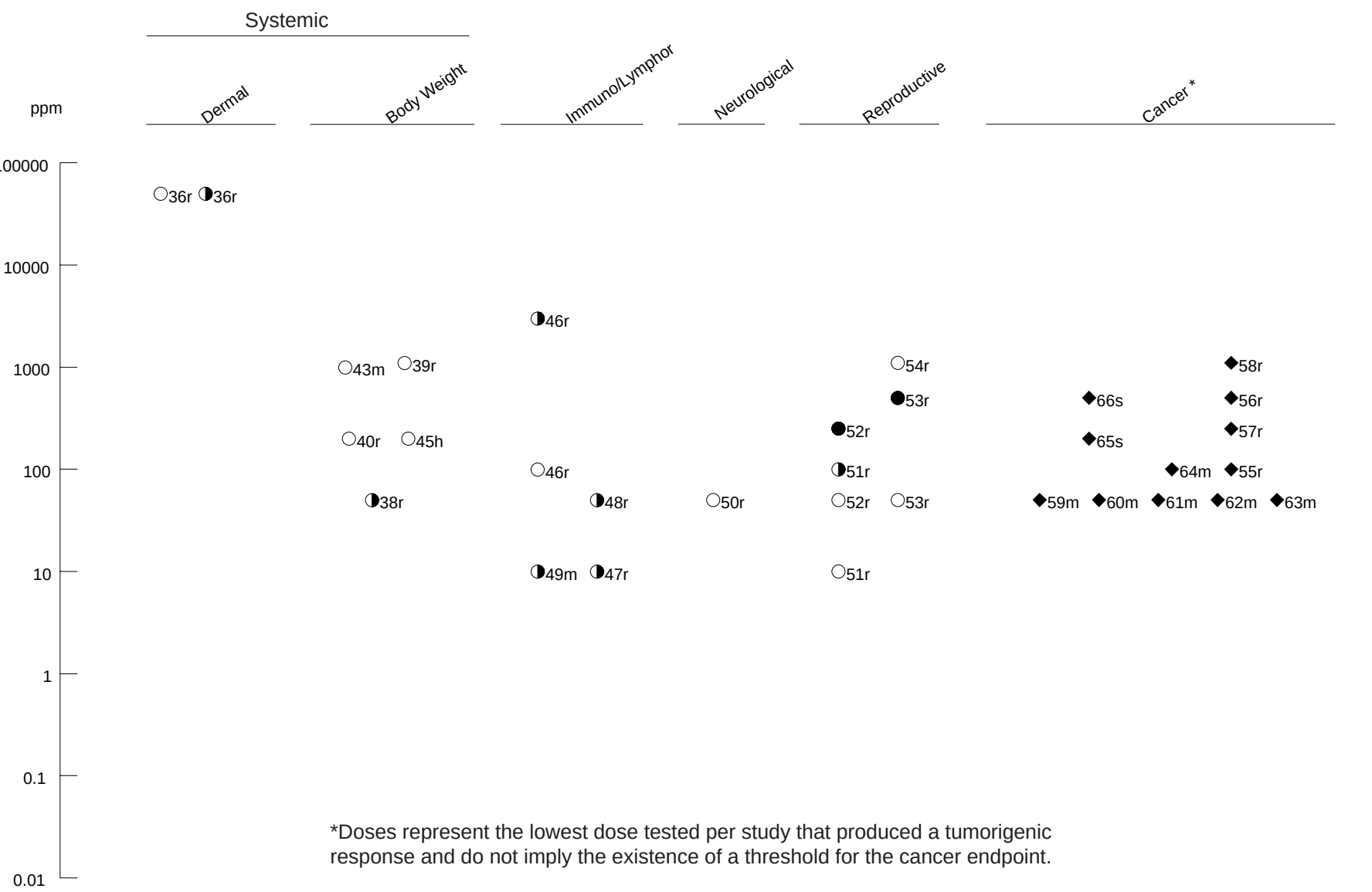
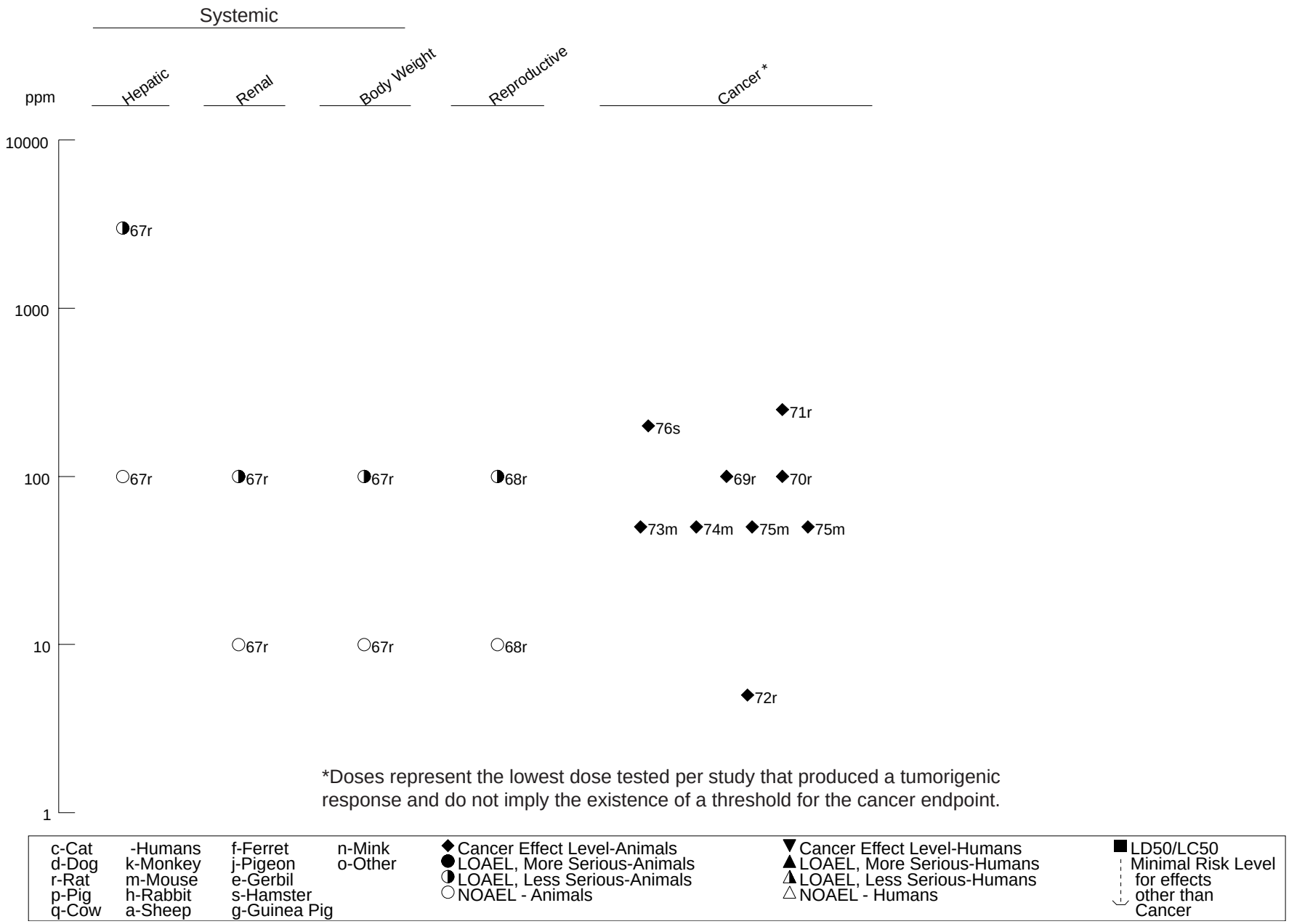


Figure 3-1. Levels of Significant Exposure to Vinyl Chloride- Inhalation (*Continued*)

Chronic (≥365 days)



Reports regarding respiratory effects in workers who are occupationally exposed to vinyl chloride are contradictory. Several epidemiologic studies found no increased incidence of respiratory disease among vinyl chloride workers (Gamble et al. 1976; Laplanche et al. 1987, 1992; NIOSH 1977). However, adverse respiratory effects were reported in several epidemiologic surveys and case reports, with these effects including increased incidence of emphysema (Suciu et al. 1975; Wong et al. 1991), decreased respiratory volume and vital capacity, respiratory insufficiency (Suciu et al. 1975), decreased respiratory oxygen and carbon dioxide transfer (Lloyd et al. 1984), pulmonary fibrosis of the linear type (Suciu et al. 1975), abnormal chest x-rays (Lilis et al. 1975, 1976), and dyspnea (Walker 1976). Interpretation of many of these results is confounded by the inclusion of smokers among those exposed to vinyl chloride and the concurrent exposure of many vinyl chloride workers to PVC resin dust, which is known to produce respiratory lesions (Mastrangelo et al. 1979).

Brief inhalation of high concentrations of vinyl chloride produced respiratory inflammation in a variety of animals. A 30-minute exposure of guinea pigs, mice, and rats to 100,000 ppm of vinyl chloride produced hyperemia in all three species (Mastromatteo et al. 1960). Exposure to higher concentrations (200,000 ppm and 300,000 ppm) produced increased congestion, edema, and at the highest concentrations, pulmonary hemorrhages in all three species (Mastromatteo et al. 1960). Tracheal epithelium was also absent in one guinea pig exposed to 400,000 ppm for 30 minutes (Mastromatteo et al. 1960). Edema and congestion of the lungs of rats were also observed following a 2-hour exposure to 150,000 ppm (Lester et al. 1963).

Histopathologic examination of mice exposed to 2,500 ppm vinyl chloride 5 hours/day, 5 days/week for 5–6 months revealed proliferation and hypertrophy of the bronchiolar epithelium, hyperplasia of the alveolar epithelium, hypersecretion of mucin (Suzuki 1978, 1980, 1981), increased endoplasmic reticulum and free ribosomes in Clara cells, and mobilization of alveolar macrophages (Suzuki 1980). These changes were observed irrespective of the recovery period (2 or 37 days), indicating that they were not readily reversible. However, these studies were severely limited by the small number of animals tested and the absence of a statistical analysis.

Chronic exposure of rats to 5,000 ppm 7 hours/day, 5 days/week for 12 months produced hyperplasia of the olfactory epithelium, increased cellularity of the interalveolar septa of the lungs, and an increased incidence of pulmonary hemorrhages (Feron and Kroes 1979). Interstitial pneumonia and hemorrhagic lungs were observed in rats exposed to 30,000 ppm of vinyl chloride 4 hours/day, 5 days/week for

12 months (Viola et al. 1971). However, the statistical significance of the findings in the studies by Feron and Kroes (1979) and Viola et al. (1971) is unknown.

Cardiovascular Effects. Occupational exposure to vinyl chloride has been associated with the development of Raynaud's phenomenon, a condition in which the fingers blanch and become numb with discomfort upon exposure to the cold. This condition has been reported most frequently among workers who cleaned the reactor tanks, a job which reportedly exposed workers to very high levels of vinyl chloride. It has also been reported in a worker exposed once to a vinyl chloride leak (Ostlere et al. 1992). Although only a small percentage of vinyl chloride workers develop Raynaud's phenomenon (Laplanche et al. 1987, 1992; Lilis et al. 1975; Marsteller et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1975; Walker 1976), the incidence is significantly higher than in unexposed workers (Laplanche et al. 1987, 1992). Investigation of the peripheral circulation of workers afflicted with Raynaud's phenomenon has revealed thickening of the walls of the digital arteries (Harris and Adams 1967), narrowing of the arterial lumen (Veltman et al. 1975), vascular occlusions (Walker 1976), arterial occlusions (Preston et al. 1976; Veltman et al. 1975), tortuosity (Preston et al. 1976), hypervascularity (Preston et al. 1976), inflammatory infiltration of the arterioles (Magnavita et al. 1986), deposition of immune products along the vascular endothelium (Ward 1976), vasomotor impairment (Suciu et al. 1963), and impaired capillary microcirculation (Magnavita et al. 1986; Maricq et al. 1976). Three reports indicate that upon removal from exposure, Raynaud's phenomenon gradually disappears (Freudiger et al. 1988; Suciu et al. 1963, 1975). For further discussion of Raynaud's phenomenon, see Immunological/Lymphoreticular Effects (Section 3.2.1.3).

Splenomegaly, with evidence of portal hypertension (dilated peritoneal veins and esophageal varices), has been reported by investigators studying the effects of vinyl chloride exposure (Marsteller et al. 1975). In addition, hypertension among vinyl chloride workers (NIOSH 1977; Suciu et al. 1975) and significantly increased mortality rate due to cardiovascular and cerebrovascular disease (Byren et al. 1976) have been reported. An association between vinyl chloride exposure and arterial hypertension was observed in an occupational worker study. Conclusive evidence was not provided for an effect of vinyl chloride on coronary heart disease (Kotseva 1996).

Investigators studying the anesthetic properties of vinyl chloride in dogs have observed that doses producing anesthesia (100,000 ppm, Oster et al. 1947; 150,000–900,000 ppm, Carr et al. 1949) also produced cardiac arrhythmias. Arrhythmias were characterized by intermittent tachycardia, extraventricular systoles, vagal beats, ventricular fibrillation, and atrioventricular block. However, the

statistical significance of these effects was not reported. At high concentrations (>30,000 ppm), vinyl chloride was been shown to sensitize the heart to epinephrine, resulting in cardiac arrhythmias in dogs (Clark and Tinston 1973). No histopathological changes in the heart were noted in guinea pigs exposed to 400,000 ppm of vinyl chloride for 30 minutes (Mastromatteo et al. 1960).

A study by Bi et al. (1985) demonstrated an increase in the relative heart weight at concentrations of vinyl chloride as low as 10 ppm when administered to male rats 6 hours/day, 6 days/week for 6 months. Heart weight was also increased after 3 months in rats exposed to 100 ppm under this regimen (Bi et al. 1985). Chronic exposure of rats to 5,000 ppm vinyl chloride 7 hours/day, 5 days/week for 1 year resulted in increases in areas of myodegeneration in the heart and thickening of the walls of arteries (Feron and Kroes 1979). However, the statistical significance of this effect was not reported. Exposure of rats to 30,000 ppm of vinyl chloride 4 hours/day, 5 days/week for 1 year also produced thickening of the walls of small arterial vessels. The thickening was characterized by a proliferation of the endothelium. In some vessels, the thickening was severe enough to cause blockage of the lumen (Viola 1970).

Gastrointestinal Effects. Approximately 32% of the vinyl chloride workers examined by Lilis et al. (1975) reported a history of "gastritis, ulcers (gastric and duodenal), and upper gastrointestinal bleeding." Because these subjects were not compared to workers who had not been exposed to vinyl chloride, the significance of these findings is unknown. Other symptoms reported by vinyl chloride workers included nausea, abdominal distension, and heartburn. Loss of appetite and nausea have been reported in Singapore workers exposed to 1–21 ppm vinyl chloride (Ho et al. 1991). However, these workers were selected on the basis of liver dysfunction.

No studies were located regarding gastrointestinal effects in animals following inhalation exposure to vinyl chloride.

Hematological Effects. Blood tests performed at autopsy of two workers whose deaths were believed to be due to exposure to extremely high levels of vinyl chloride revealed that blood clotting did not occur (Danziger 1960). Slight-to-severe thrombocytopenia in workers occupationally exposed to vinyl chloride was reported in several studies (Marsteller et al. 1975; Micu et al. 1985; Veltman et al. 1975), but Lilis et al. (1975) found no increased incidence of thrombocytopenia in vinyl chloride workers. A prospective study of female workers exposed to vinyl chloride at levels ranging from 0.2 to 130.7 ppm showed that the exposed workers had a significantly lower number of platelets than the nonexposed controls during the early part of their pregnancies (weeks 8–10) but that this effect abated by the end of

the pregnancy (34–38 weeks) following a period free from exposure (Bao et al. 1988). Splenomegaly was reported in a number of studies (Ho et al. 1991; Marsteller et al. 1975; Popper and Thomas 1975; Suciu et al. 1963; Veltman et al. 1975). Thrombocytopenia was found in patients who both did and did not present with splenomegaly (Veltman et al. 1975). Increased levels of two plasma proteins (α_1- and α_2-globulin) were reported in studies examining the effects of occupational exposure to vinyl chloride (Harris and Adams 1967; Suciu et al. 1975).

A brief (30-minute) exposure of guinea pigs to 400,000 ppm vinyl chloride resulted in a failure of the blood to clot in the animals that died during the exposure (Mastromatteo et al. 1960). Mice that were exposed to 5,000 ppm (4 hours/day for 6 days) or 10,000 ppm (4 hours/day for 5 days) showed an increased emergence of basophilic stippled erythrocytes (Kudo et al. 1990). This effect was also noted in mice that were exposed for 10 weeks to 50 ppm intermittently (4 hours/day for 4–5 days/week,) or to 30–40 ppm continuously for 62 days (Kudo et al. 1990). Exposure of dogs and rats to 200 ppm for 7 hours/day, 5 days/week, for 6 months had no effect on hematologic values (Torkelson et al. 1961). Also, an 8-week exposure of mice to 1,000 ppm for 6 hours/day, 5 days/week had no effect on erythrocyte or leukocyte counts (Sharma and Gehring 1979). Exposure of rats to either 50,000 ppm for 8 hours/day for 19 consecutive days or 20,000 ppm for 8 hours/day, 5 days/week for 92 days resulted in a decrease in white blood cells (Lester et al. 1963). Exposure of rats to 5,000 ppm vinyl chloride for 7 hours/day, 5 days/week for 1 year produced increased hematopoiesis in the spleen (Feron and Kroes 1979). The statistical significance of these results was not provided. Blood clotting time was decreased in rats exposed to 5,000 ppm for7 hours/day for 1 year, but the statistical significance of these effects was not reported (Feron et al. 1979a).

Musculoskeletal Effects. Acroosteolysis, or resorption of the terminal phalanges of the finger, was observed in a small percentage of workers occupationally exposed to vinyl chloride (Dinman et al. 1971; Lilis et al. 1975; Marsteller et al. 1975; Sakabe 1975; Veltman et al. 1975; Wilson et al. 1967). As with Raynaud's phenomenon, acroosteolysis was reported predominantly among polymerization tank cleaners. Bone lesions were most often confined to the terminal phalanges of the fingers, but in a few cases the bones of the toes (Harris and Adams 1967), feet (Preston et al. 1976), sacroiliac joint (Harris and Adams 1967), and arms, legs, pelvis, and mandible (Preston et al. 1976) were also involved. Development of acroosteolysis was most often preceded by Raynaud's phenomenon (Dinman et al. 1971; Freudiger et al. 1988; Harris and Adams 1967; Magnavita et al. 1986; Markowitz et al. 1972; Preston et al. 1976; Sakabe 1975; Veltman et al. 1975; Wilson et al. 1967). In two reports, bone resorption was observed to progress despite discontinuation of exposure (Markowitz et al. 1972; Preston et al. 1976). However, in two other

reports, improvement was observed after exposure ceased (Veltman et al. 1975; Wilson et al. 1967). Joint pain was also reported by Lilis et al. (1975).

Although Sokal et al. (1980) found no alterations in the bones of male rats exposed to 20,000 ppm for 5 hours/day, 5 days/week for 10 months, Viola (1970) observed skeletal changes (i.e., osteochondroma) in the bones of rats exposed to 30,000 ppm for 4 hours/day, 5 days/week for 12 months. The statistical significance of these effects was not reported and only one exposure level was tested.

Hepatic Effects. Throughout the early years of the use of vinyl chloride, workers experienced only a minimal degree of functional hepatic abnormalities. However, when it became apparent in the early 1970s that angiosarcoma of the liver was associated with long-term vinyl chloride exposure, an intensive effort was initiated by a number of investigators to characterize the hepatic effects of vinyl chloride. These studies revealed characteristic hepatic lesions produced by vinyl chloride exposure (Berk et al. 1975; Falk et al. 1974; Gedigke et al. 1975; Ho et al. 1991; Jones and Smith 1982; Lilis et al. 1975; Liss et al. 1985; Marsteller et al. 1975; NIOSH 1977; Popper and Thomas 1975; Suciu et al. 1975; Tamburro et al. 1984; Vihko et al. 1984). The incidence and severity of the effects correlated well with the duration of exposure (Gedigke et al. 1975; Lilis et al. 1975; NIOSH 1977).

Routine noninvasive techniques revealed hepatomegaly in a limited number of workers (14–37%) (Ho et al. 1991; Lilis et al. 1975; Marsteller et al. 1975; NIOSH 1977; Suciu et al. 1963, 1975). However, when peritoneoscopy was performed or biopsies were obtained from exposed workers, Marsteller et al. (1975) found a much higher prevalence of hepatic abnormalities. Only 37% of the workers studied by Marsteller et al. (1975) were diagnosed with hepatomegaly, but peritoneoscopy revealed a 50% incidence of granular changes in the liver surface and an 86% incidence of capsular fibrosis with increased numbers of capsular vessels. Histopathological examination of the biopsied tissue from these workers revealed an 80% incidence of collagenization of the sinusoidal walls, a 90% incidence of proliferation of cells lining the sinusoids, a 30% incidence of septal fibrosis, and degeneration of hepatocytes (incidence not specified). A number of other investigators observed similar changes in liver tissues obtained from workers exposed to vinyl chloride (Falk et al. 1974; Gedigke et al. 1975; Popper and Thomas 1975; Tamburro et al. 1984). Based on these observations, a profile of vinyl chloride-induced liver damage was compiled and includes the following features: hypertrophy and hyperplasia of hepatocytes, activation and hyperplasia of sinusoidal lining cells, fibrosis of the portal tracts and the septa and intralobular perisinusoidal regions, sinusoidal dilation, and focal areas of hepatocellular degeneration. This pattern of changes was observed to be highly unusual and was similar to the hepatic changes produced by arsenic (Gedigke et al. 1975). In

addition, the degenerative changes in hepatocytes appeared to be less severe when biopsy material was obtained from workers who had not been exposed to vinyl chloride recently. However, sinusoidal changes were not influenced by the length of time since the last exposure (Gedigke et al. 1975).

One possible reason that the hepatotoxic effects of vinyl chloride went undetected for many years was the lack of sensitivity of standard biochemical liver function tests to detect the liver injury produced by vinyl chloride (Berk et al. 1975; Marsteller et al. 1975; Tamburro et al. 1984; Vihko et al. 1984). For example, the values obtained in several standard biochemical liver function tests (activities of serum alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase) from workers with biopsy evidence of vinyl chloride-associated liver damage were not significantly higher than those from unexposed controls (Liss et al. 1985). Gamma-glutamyltransferase levels were significantly higher in workers exposed to vinyl chloride at TWA exposure concentrations of >10 ppm compared to workers exposed to lower exposure concentrations (Du et al. 1995). Workers exposed to lower levels of vinyl chloride had gamma-glutamyltransferase levels that were within the normal range (Hensyl 1990). Serum bile acids (Berk et al. 1975; Liss et al. 1985) and/or indocyanine green clearance (Liss et al. 1985; Tamburro et al. 1984) correlated with liver injury. Furthermore, investigators have shown that levels of chenodeoxycholic acid (a serum bile acid) in asymptomatic vinyl chloride workers were elevated when compared to the 95% interval of values from a healthy reference population (Vihko et al. 1984). The serum hyaluronic acid concentration was demonstrated to be elevated in workers with angiosarcoma of the liver, while other liver function tests were normal (McClain et al. 2002).

A recent IARC update of a multi-center cohort study demonstrated an increase in mortality from liver cirrhosis in workers exposed to moderate to high concentrations of vinyl chloride (Ward et al. 2001). Morbidity associated with liver cirrhosis was also reported to be elevated among vinyl chloride workers (Du and Wang 1998). Alcohol intake was not evaluated as a critical confounding factor in these studies. Liver ultrasonography illustrated an increase in the incidence of periportal fibrosis in vinyl chloride workers (Maroni et al. 2003). Portal fibrosis and portal hypertension were considered to contribute to mortality in several cases (Lee et al. 1996; Lelbach 1996). Abnormal liver function was demonstrated in workers exposed to low concentrations of both vinyl chloride and ethylene dichloride (Cheng et al. 1999).

Brief exposure of animals to extremely high concentrations of vinyl chloride has been shown to produce hepatic damage. For example, acute exposure (30 minutes) of guinea pigs and mice to 300,000 ppm of vinyl chloride produced liver congestion or severe fatty degeneration while 200,000 ppm caused fatty infiltration in rats (Mastromatteo et al. 1960). Exposure to 100,000 ppm for 6 hours produced

centrilobular vacuolization and increased alanine serum α-ketoglutarate transaminase activity in rats (Jaeger et al. 1974). However, exposure of rats to 50,000 ppm for 6 hours produced no observable effects on the liver (Reynolds et al. 1975a, 1975b). In contrast, a single-concentration study in which pregnant rats were continuously exposed to 1,500 ppm for 7–9 days during either the first or second trimester of pregnancy resulted in an increase in the liver-to-body-weight ratio (Ungvary et al. 1978). Interestingly, a single 1-hour exposure of mice to 500, 5,000, or 50,000 ppm of vinyl chloride, followed by an 18-month observation period, resulted in an increased incidence of hepatocellular hypertrophy in these animals at terminal sacrifice (Hehir et al. 1981). The hypertrophy was not dose dependent; thus, the significance of this effect is uncertain.

In studies with longer durations of exposure, lower concentrations of vinyl chloride have produced hepatic toxicity. Symptoms of hepatotoxicity that have been observed in rats have included hepatocellular degeneration (Sokal et al. 1980; Torkelson et al. 1961; Wisniewska-Knypl et al. 1980), swelling of hepatocytes with compression of sinusoids (Lester et al. 1963), dilation of the rough endoplasmic reticulum (Du et al. 1979), proliferation (Sokal et al. 1980) or hypertrophy (Thornton et al. 2002; Wisniewska-Knypl et al. 1980) of smooth endoplasmic reticulum, changes in metabolic enzyme activities (Du et al. 1979; Wisniewska-Knypl et al. 1980), proliferation of reticulocytes (Sokal et al. 1980), and an increased liver-to-body-weight ratio (Bi et al. 1985; Lester et al. 1963; Sokal et al. 1980; Thornton et al. 2002; Torkelson et al. 1961). For example, exposure of rats to 500 ppm for 7 hours/day, 5 days/week for 4.5 months resulted in an increase in liver-to-body-weight ratio and granular degeneration (Torkelson et al. 1961). An increased liver-to-body-weight ratio was also found in rats exposed to 100 ppm vinyl chloride for 7 hours/day, 5 days/week for 6 months (Torkelson et al. 1961). Relative liver weight was decreased in mice exposed to 1,000 ppm vinyl chloride for 6 hours/day, 5 days/week for 8 weeks (Sharma and Gehring 1979). The liver-to-body-weight ratio was shown to be increased in male rats exposed to 3,000 ppm but not 100 ppm, vinyl chloride for 6 hours/day, 5 days/week for 12 months (Bi et al. 1985). Significantly increased liver-to-body-weight ratio was also observed in rats exposed to concentrations of vinyl chloride as low as 10 ppm for 6 hours/day, 6 days/week for 6 months (Bi et al. 1985). Exposure of rats to 500 ppm for 5 hours/day, 5 days/week for 10 months produced swelling of hepatocytes and proliferation of reticuloendothelial cells, increased liver weight, and cellular degeneration; at 50 ppm, small lipid droplets and proliferation of smooth endoplasmic reticulum were noted (Sokal et al. 1980). Histopathological examination of rats exposed to either 50,000 ppm vinyl chloride for 8 hours/day for 19 consecutive days or 20,000 ppm vinyl chloride for 8 hours/day, 5 days/week, for 92 days showed hepatocellular hypertrophy, vacuolization, and sinusoidal compression (Lester et al. 1963). Mice exposed to 2,500 ppm vinyl chloride 5 hours/day, 5 days/week for up to

6 months showed histopathological changes in the liver that included hyperplasia of hepatocytes and activated sinusoidal cells (Schaffner 1978). Centrilobular necrosis and degeneration were noted in rabbits exposed to 200 ppm vinyl chloride 7 hours/day, 5 days/week for 6 months but not at 100 ppm vinyl chloride in this regimen (Torkelson et al. 1961). Also, exposure of rats to 50 ppm for 5 hours/day, 5 days/week for 10 months produced fatty degeneration and proliferation of the smooth endoplasmic reticulum (Wisniewska-Knypl et al. 1980). Liver effects were observed in a 2-generation reproductive toxicity study where rats were exposed to 0, 10, 100, or 1,100 ppm vinyl chloride (6 hours/day for a 10-week premating period and a 3-week mating period) (Thornton et al. 2002). Absolute and relative mean liver weights were significantly increased at all exposure levels in F_0 males and in 100- and 1,100-ppm F_1 males. Centrilobular hypertrophy, considered to be a minimal adverse effect, was noted in the livers of all 1,100-ppm male and female F_0 and F_1 rats, most 100-ppm male and female F_0 and F_1 rats, and in 2/30 and 6/30 of the 10-ppm F_0 male and F_1 female rats, respectively. Centrilobular hypertrophy was not noted in the 30 female rats of the control group. Histopathological alterations occurring at 100 and 1,100 ppm included centrilobular hypertrophy and acidophilic, basophilic, and clear cell foci. Based on this study, an intermediate-duration MRL of 0.03 ppm was calculated as described in the footnote in Table 3-1. No chronic-duration inhalation MRL was derived for vinyl chloride because of the absence of a suitable LOAEL or NOAEL for derivation. A NOAEL (10 ppm) and a LOAEL (100 ppm) were identified for testicular effects (increases in the number of degenerative seminiferous tubule changes) in a chronic-duration inhalation study (Bi et al. 1985). However, these data were not used as the basis of a chronic-duration inhalation MRL because the LOAEL for these effects was higher than the LOAEL of 10 ppm for nonneoplastic liver lesions identified in the intermediate-duration rat inhalation study of Thornton et al. (2002). Bi et al. (1985) does not report the incidence of histopathological changes in the liver following chronic inhalation exposure; however, the results of the Thornton et al. (2002) study suggest that liver effects would occur at lower doses than the reported testicular effects. No other chronic-duration inhalation toxicity studies were located in which vinyl chloride-induced nonneoplastic lesions were described.

The NOAELs for liver effects in a number of species following a 6-month exposure to vinyl chloride indicated that mice and rats were the most sensitive (NOAEL=50 ppm), rabbits were the next most sensitive (NOAEL=100 ppm), and dogs and guinea pigs were the least sensitive (NOAEL>200 ppm) (Torkelson et al. 1961).

Popper et al. (1981) compared histopathological findings from sections of liver from mice and rats exposed by Maltoni and LeFemine (1975) with the liver biopsy material obtained from vinyl chloride

workers. Hyperplasia and hypertrophy of hepatocytes and/or sinusoidal cells, with areas of sinusoidal dilation, were observed in both humans and rodents. The major difference between the species was the greater degree of fibrosis, seen as reticulin deposition and collagen formation, in the livers of humans. Also, inflammatory cells were present in the livers of humans but not of rodents.

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to vinyl chloride.

Acute exposure of mice and rats to 300,000 ppm of vinyl chloride for 30 minutes resulted in kidney congestion (Mastromatteo et al. 1960). Also, the kidneys of one mouse out of five exposed to either 100,000 or 200,000 ppm of vinyl chloride for 30 minutes showed degenerative changes (Mastromatteo et al. 1960). Exposure of rats to 50,000 ppm for 8 hours/day for 19 consecutive days or 20,000 ppm for 8 hours/day, 5 days/week for 92 days produced no adverse effects on the kidneys (Lester et al. 1963). However, exposures of male rats to 3,000 ppm for 6 hours/day, 6 days/week, for 3 months produced an increase in the kidneys-to-body-weight ratio (Bi et al. 1985). After a 6-month observation period, there was also an increased kidneys-to-body-weight ratio noted in the male rats exposed to 100 ppm vinyl chloride for 6 hours/day, 6 days/week for 12 months; no effect was noted at 10 ppm (Bi et al. 1985). Relative kidney weights was increased in male rats exposed to 500 ppm vinyl chloride for 5 hours/day, 5 days/week, for 10 months, although no histopathological changes in the kidney were noted (Sokal et al. 1980). No changes in kidney weights were reported when mice were exposed to 1,000 ppm vinyl chloride 6 hours/day, 5 days/week for 8 weeks (Sharma and Gehring 1979). Urinalysis values were within normal limits in rats and rabbits exposed to 200 ppm vinyl chloride for up to 7 hours/day, 5 days/week, for 6 months (Torkelson et al. 1961). One year of exposure to 5,000 ppm vinyl chloride for 7 hours/day, 5 days/week produced an increase in the kidneys-to-body-weight ratio (Feron et al. 1979a) and tubular nephrosis in rats (Feron and Kroes 1979). However, the statistical significance of these findings was not provided in the study.

Endocrine Effects. A study of workers exposed to vinyl chloride in PVC manufacturing plants reported that most workers who presented with scleroderma were shown to have thyroid insufficiency (Suciu et al. 1963).

No histopathological effects on the adrenals were reported in guinea pigs exposed to 400,000 ppm for 30 minutes (Mastromatteo et al. 1960). Rats exposed to 30,000 ppm vinyl chloride 4 hours/day,

5 days/week for 12 months were found to have colloid goiter and markedly increased numbers of perifollicular cells (Viola 1970).

Dermal Effects. Occupational exposure to vinyl chloride was observed to produce scleroderma-like skin changes on the hands of a small percentage of exposed workers (Freudiger et al. 1988; Lilis et al. 1975; Marsteller et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1975; Walker 1976). The skin changes were characterized by a thickening of the skin (Lilis et al. 1975; Markowitz et al. 1972; Ostlere et al. 1992; Preston et al. 1976; Veltman et al. 1975; Walker 1976), decreased elasticity (Lilis et al. 1975), and edema (Lilis et al. 1975; Suciu et al. 1975) and were almost exclusively observed in exposed individuals who also suffered from Raynaud's phenomenon. Skin biopsies revealed increased collagen bundles in the subepidermal layer of the skin (Harris and Adams 1967; Markowitz et al. 1972; Ostlere et al. 1992; Veltman et al. 1975). Biochemical analyses by Jayson et al. (1976) demonstrated that a high rate of collagen synthesis was taking place in the affected skin. Most often the skin changes were confined to the hands and wrists, but Jayson et al. (1976) reported scleroderma-like skin changes on the hands, arms, chest, and face of one afflicted worker.

Skin changes were observed in rats exposed to 30,000 ppm for 12 months (Viola 1970). The skin of the paws of the exposed rats showed areas of hyperkeratosis, thickening of the epidermis, edema, collagen dissociation, and fragmentation of the elastic reticulum. Interpretation of these results is limited by the absence of a statistical analysis and insufficient information on the treatment of control animals. Lester et al. (1963) reported that male rats exposed to 50,000 ppm vinyl chloride 8 hours/day for 19 days had thin coats and scaly tails, while females exposed to the same concentration showed no effects. For further information regarding scleroderma-like responses to vinyl chloride exposure, see Cardiovascular Effects (Section 3.2.1.2) and Immunological and Lymphoreticular Effects (Section 3.2.1.3).

Ocular Effects. Ocular effects that have been reported after inhalation exposure are believed to have resulted from direct contact of the vinyl chloride gas with the eyes and are discussed under Dermal Exposure (Section 3.2.3.2). No studies were located regarding ocular effects in humans that were related solely to the inhalation of vinyl chloride. No histopathological changes were noted in the eyes of guinea pigs exposed to 400,000 ppm vinyl chloride for 30 minutes (Mastromatteo et al. 1960).

Body Weight Effects. Several studies have reported that workers intoxicated by vinyl chloride experienced anorexia (Suciu et al. 1963, 1975).

No effects on body weight were noted in ICR mice exposed to either 10,000 ppm vinyl chloride 4 hours/day for 5 days or to 5,000 ppm vinyl chloride 4 hours/day for 6 days (Kudo et al. 1990). No consistent or dose-related differences in body weight were noted between control rats and rats exposed to up to 50,000 ppm for 1 hour or rats exposed to 500 ppm 5 days/week, for 2 weeks (Hehir et al. 1981). However, statistical analysis was not performed. No changes in body weight gain were noted in rats or rabbits exposed to 200 ppm vinyl chloride 7 hours/day, 5 days/week for 6 months (Torkelson et al. 1961) or in mice exposed to 1,000 ppm vinyl chloride 6 hours/day, 5 days/week for 8 weeks (Sharma and Gehring 1979). Significant decreases were found in the body weight of rats exposed to 100 ppm vinyl chloride 6 hours/day, 6 days/week for 12 months; these changes were not observed at 10 ppm (Bi et al. 1985). Significant decreases were also noted in mean body weights of rats exposed to 5,000 ppm vinyl chloride 7 hours/day, 5 days/week for 4–52 weeks but these data were not quantified (Feron et al. 1979a). This study was limited since only one concentration was tested. Body weight was decreased 10% in male rats exposed to 50 ppm vinyl chloride 5 hours/day, 5 days/week for 10 months (Sokal et al. 1980). Maternal body weight gain was significantly decreased in mice exposed to 500 ppm for 7 hours/day during gestation days (Gd) 6–15 (John et al. 1977).

3.2.1.3 Immunological and Lymphoreticular Effects

A number of studies have examined the immunologic profiles of workers occupationally exposed to vinyl chloride. Male workers exposed to vinyl chloride for an average of 8 years, with concentrations ranging from 1 to 300 ppm during sampling periods, were found to have significantly increased percentages of lymphocytes compared to controls (Fucic et al. 1995, 1997, 1998). Additionally, 75 out of these 100 workers showed disturbances of mitotic activity in these cells. A statistically significant increase in circulating immune complexes in workers exposed to vinyl chloride was observed when compared to levels in unexposed workers (Bogdanikowa and Zawilska 1984). The increase in circulating immune complexes was greatest in women and in those with duties involving exposure to relatively higher levels of vinyl chloride. Compared to controls, immunoglobulin G (IgG) levels were significantly increased in women exposed to the high levels of vinyl chloride in the same study.

Studies of workers who have developed "vinyl chloride disease," a syndrome consisting of Raynaud's phenomenon, acroosteolysis, joint and muscle pain, enhanced collagen deposition, stiffness of the hands, and scleroderma-like skin changes, indicate that this disease may have an immunologic basis. Sera obtained from patients with varying degrees of severity of symptoms of vinyl chloride disease

demonstrate a close correlation between the disease severity and the extent of the immunologic abnormality (Grainger et al. 1980; Langauer-Lewowicka et al. 1976; Ward 1976), although these symptoms have been reported without immunological findings (Black et al. 1986; Ostlere et al. 1992). The most frequent immunologic finding in workers with vinyl chloride disease is an increase in circulating immune complexes or cryoglobulinemia. In workers with the most severe clinical signs, there also are an increased incidence of B-cell proliferation, hyperimmunoglobulinemia (Ward 1976), cryoglobulinemia (Grainger et al. 1980), and complement activation (Grainger et al. 1980; Ward 1976). Evidence of a structurally altered IgG has been obtained, and it has been proposed that vinyl chloride (or a metabolite) binds to IgG (Grainger et al. 1980).

Based on the similarity of vinyl chloride disease and systemic sclerosis, which may be a genetically linked autoimmune disease, Black et al. (1983, 1986) examined the human lymphocyte antigen (HLA) phenotypes of patients with vinyl chloride disease. Many autoimmune diseases show statistically significant associations with certain HLA alleles. These authors found that when compared to unexposed controls or asymptomatic controls, workers with vinyl chloride disease had a significantly greater incidence of possessing the HLA-DR5 allele. Furthermore, among those with the disease, the severity of the symptoms was significantly related to the possession of the HLA-DR3 and B8 alleles. These authors concluded that susceptibility was increased in the presence of HLA-DR5 or a gene in linkage disequilibrium with it, and progression was favored by HLA-DR3 and B8 phenotypes. Immune system dysfunction has also been linked to a case of polymyositis (i.e., muscle fiber necrosis and atrophy) in an exposed worker, with involvement of antibodies to histidyl-t-RNA synthetase (Jo-1) (Serratrice et al. 2001).

Splenomegaly was reported in a number of studies (Ho et al. 1991; Marsteller et al. 1975; Popper and Thomas 1975; Suciu et al. 1963; Veltman et al. 1975). No histopathological changes were noted in the spleen or lymph nodes of guinea pigs exposed to 400,000 ppm vinyl chloride for 30 minutes (Mastromatteo et al. 1960). An increase in the relative spleen weight was observed in rats exposed to 50 ppm for 5 hours/day, 5 days/week for 10 months (Sokal et al. 1980). Although no dose response was evident, increased relative spleen weight was also reported by Bi et al. (1985) when rats were exposed to either 10 ppm for 6 hours/day, 6 days/week for 6 months or 3,000 ppm for 6 hours/day, 6 days/week for 3 months. This effect was not observed at 100 ppm in the 3-month study (Bi et al. 1985).

The immunologic effects of vinyl chloride have been examined in mice (Sharma and Gehring 1979). Lymphocytes isolated from the spleens of mice exposed to concentrations as low as 10 ppm vinyl

chloride 6 hours/day, 5 days/week for 4 weeks had increased spontaneous and lectin-stimulated transformation. This increase was not observed when lymphocytes from unexposed mice were cultured in the presence of vinyl chloride.

The highest NOAEL value and all reliable LOAEL values for immunological effects in guinea pigs, mice, and rats exposed in acute- and intermediate-duration studies are recorded in Table 3-1 and plotted in Figure 3-1. For further information on Raynaud's phenomenon and scleroderma-like responses to vinyl chloride, see Cardiovascular and Dermal Effects (Section 3.2.1.2).

3.2.1.4 Neurological Effects

Vinyl chloride was once considered for use as an inhalation anesthetic (ACGIH 2003). Investigators studying the effects of vinyl chloride exposure frequently report central nervous system symptoms that are consistent with the anesthetic properties of vinyl chloride. The most commonly reported central nervous system effects are ataxia or dizziness (Ho et al. 1991; Langauer-Lewowicka et al. 1983; Lilis et al. 1975; Marsteller et al. 1975; Spirtas et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1975), drowsiness or fatigue (Langauer-Lewowicka et al. 1983; Spirtas et al. 1975; Suciu et al. 1963, 1975; Walker 1976), loss of consciousness (NIOSH 1977), and/or headache (Langauer-Lewowicka et al. 1983; Lilis et al. 1975; Marsteller et al. 1975; NIOSH 1977; Spirtas et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1975). Other central nervous system effects that have been reported by vinyl chloride workers include euphoria and irritability (Suciu et al. 1963, 1975), visual and/or hearing disturbances (Marsteller et al. 1975), nausea (Marsteller et al. 1975; Spirtas et al. 1975), memory loss (Langauer-Lewowicka et al. 1983; Suciu et al. 1963, 1975), and nervousness and sleep disturbances (Langauer-Lewowicka et al. 1983; Suciu et al. 1963). Central nervous system tests revealed pyramidal signs and cerebellar disturbances in some exposed subjects (Langauer-Lewowicka et al. 1983); however, reliable estimates of exposure levels producing these effects were not available.

Exposure of volunteers to known levels of vinyl chloride has provided some indication of the levels of vinyl chloride associated with the effects noted above. Volunteers exposed to 25,000 ppm vinyl chloride for 3 minutes, in a single-exposure study, reported experiencing dizziness, disorientation, and burning sensations in the feet during exposure (Patty et al. 1930). Recovery from these effects was rapid upon termination of exposure, but the subjects developed headaches. Exposure of volunteers to concentrations of vinyl chloride ranging from 4,000 to 20,000 ppm for 5 minutes twice a day in periods separated by

6 hours on 3 consecutive days was studied by Lester et al. (1963). No effects were noted at 4,000 ppm. However, at 8,000 ppm one of six subjects reported feeling dizzy. The incidence of dizziness increased at higher concentrations. Nausea was experienced at higher concentrations, and recovery from all effects was rapid upon termination of exposure. Headaches developed following exposure to 20,000 ppm.

Indications of an exposure-related peripheral neuropathy have been observed in a number of the occupational studies. A peripheral neuropathy, most severe in hands and feet, was diagnosed in 70% of the vinyl chloride workers examined in a study by Perticoni et al. (1986). The peripheral neuropathy was manifested as denervation-related fasciculations and fibrillations and increased duration and amplitude of motor unit potentials (indicating collateral sprouting). Similar effects were observed by Magnavita et al. (1986) in a case study of a vinyl chloride worker. Other peripheral nervous system symptoms have been reported by a number of investigators studying the effects of occupational exposure to vinyl chloride. The symptom most frequently reported was tingling (paresthesia) in the extremities (Lilis et al. 1975; Sakabe 1975; Spirtas et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1975; Walker 1976). Additional peripheral nervous system symptoms included numbness in the fingers (Lilis et al. 1975; Sakabe 1975), weakness (Langauer-Lewowicka et al. 1983; Suciu et al. 1963, 1975), depressed reflexes (NIOSH 1977), warmth in the extremities (Suciu et al. 1963, 1975), and pain in the fingers (Sakabe 1975). It is unclear whether some of these symptoms are associated with tissue anoxia due to vascular insufficiency, or whether they represent the direct toxic effects of vinyl chloride on peripheral nerves.

Acute exposure of a number of species to high levels of vinyl chloride has provided additional information on the characteristics of the central nervous system effects that are produced. Exposure of guinea pigs to 10,000 ppm for 8 hours (Patty et al. 1930) was observed to be without effects. Exposure to 25,000 ppm resulted in ataxia, which developed into unconsciousness during the 8-hour exposure. As the concentration was increased, the development of unconsciousness was more rapid. At 100,000 ppm, Mastromatteo et al. (1960) observed the development of unconsciousness within 30 minutes. Mice experienced similar signs at approximately equivalent exposure levels. At 5,000 ppm, vinyl chloride was without effect during a 1-hour exposure. Exposure to 50,000 ppm produced ataxia and twitching (Hehir et al. 1981), and at 100,000 ppm for 30 minutes, unconsciousness was produced, proceeded by increased motor activity, incoordination, twitching, and tremors (Mastromatteo et al. 1960). Similar effects in rats were observed by Lester et al. (1963), Jaeger et al. (1974), and Mastromatteo et al. (1960). In contrast, in two reports using rats, exposure to 50,000 ppm for either 1 or 6 hours was without effect (Hehir et al. 1981; Jaeger et al. 1974). No effects were noted in rats exposed to 500 ppm vinyl chloride for 2 weeks (1 hour/day, 5 days/week) or in rats exposed to 50 ppm for 20 weeks (1 hour/day, 5 days/week) (Hehir et

al. 1981). In addition, tolerance developed to the intoxicating effects of exposure to 50,000 ppm vinyl chloride after five or six 8-hour exposures (Lester et al. 1963).

Chronic exposure of rats to high levels of vinyl chloride has produced damage to nervous tissue. Rats exposed to 30,000 ppm for 4 hours/day, 5 days/week for 12 months in a single-concentration study were soporific during exposures (Viola 1970; Viola et al. 1971). Following 10 months of exposure, the rats had decreased responses to external stimuli and disturbed equilibrium. Histopathological examination revealed diffuse degeneration of gray and white matter. Cerebellar degeneration in the Purkinje cell layer was pronounced. Also, peripheral nerve endings were surrounded and infiltrated with fibrous tissue (Viola 1970; Viola et al. 1971). Nonneoplastic lesions in the brain were not noted in rats exposed to 5,000 ppm for 7 hours/day, 5 days/week for 12 months in a single-concentration study by Feron and Kroes (1979).

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species from acute- or intermediate-duration studies are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

A number of case reports of workers occupationally exposed to vinyl chloride suggest that sexual performance may be affected by vinyl chloride. However, these studies are limited by the lack of quantification of exposure levels and possible concomitant exposures to other chemicals. Sexual impotence was reported by 24% of the workers examined by Suciu et al. (1975). Approximately 20% of the workers examined by Veltman et al. (1975) complained of potency troubles. A loss of libido in 35% and impotence and decreased androgen secretion in 8% of workers exposed at least once to very high levels of vinyl chloride were also reported by Walker (1976).

In retrospective and prospective studies by Bao et al. (1988), increased incidence and severity of elevated blood pressure and edema during pregnancy (preeclampsia) were found in female workers exposed to vinyl chloride when compared to unexposed workers. Company records indicated that exposure levels ranged from 3.9 to 89.3 ppm during the retrospective study and from 0.2 to 130.7 ppm during the prospective study. More detailed information regarding the exposure levels was not presented.

A 2-generation reproductive toxicity study was conducted in rats exposed to vinyl chloride via inhalation (Thornton et al. 2002). Male and female Sprague-Dawley rats were exposed to 0, 10, 100, or 1,100 ppm vinyl chloride 6 hours/day for a 10-week premating period and a 3-week mating period. No adverse effects were noted in reproductive capability over the two generations at any dose. No effects were seen in body weight, feed consumption, ability to reproduce, gestation index or length, or pre- and postweaning developmental landmarks. Sperm counts, motility, and morphology were also unaffected by vinyl chloride exposure. Changes in liver weights and/or histopathological alterations were seen in F_0 and F_1 generation male and female rats. For further information regarding the liver toxicity of vinyl chloride, see Section 3.2.1.2.

Two dominant lethal studies examined the reproductive performance of exposed male rats. A brief exposure (5 days, 6 hours/day) of mice to concentrations of vinyl chloride as high as 30,000 ppm had no effect on male fertility or pre- or postimplantation loss (Anderson et al. 1976). In contrast, exposure of male rats to concentrations as low as 250 ppm for 6 hours/day, 5 days/week for 11 weeks produced a decrease in the ratio of pregnant to mated females, indicating a decrease in male fertility; this effect was not observed at 50 ppm (Short et al. 1977). These results are supported by two studies using rats in which adverse effects of vinyl chloride on the testes were observed (Bi et al. 1985; Sokal et al. 1980). Exposure of rats to 100 ppm for 6 hours/day, 6 days/week for 12 months produced a significant increase in the incidence of damage to the seminiferous tubules and depletion of spermatocytes (Bi et al. 1985). At the 6-month interim sacrifice, a significant decrease in testicular weight was also observed at 100 ppm. No effect on male reproductive organs was observed in this study at 10 ppm. A significant increase in damage to the spermatogenic epithelium and disorders of spermatogenesis were found with exposure to 500 ppm vinyl chloride for 5 hours/day, 5 days/week for 10 months, but was not observed after exposure to 50 ppm vinyl chloride (Sokal et al. 1980). No significant change in testicular weight was found in rats exposed to 500 ppm for 7 hours/day, 5 days/week for 4.5 months or in dogs, rabbits, or guinea pigs exposed to 200 ppm for 7 hours/day, 5 days/week for 6 months (Torkelson et al. 1961). However, the quality of this study is limited because of the small number of animals tested. Exposures involved up to 10 rats or guinea pigs of each gender, three rabbits of each sex, and one dog of each sex. No histopathological data on the testes of these animals were presented.

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

Although evidence has been presented indicating that members of communities with nearby vinyl chloride polymerization facilities have significantly greater incidences of some forms of developmental toxicity, these studies failed to demonstrate a statistically significant correlation between the developmental toxicity and either parental occupation or proximity to the facility (Edmonds et al. 1978; Infante 1976; Rosenman et al. 1989; Theriault et al. 1983).

The pregnancy outcome of wives of workers employed at a vinyl chloride polymerization facility was compared to the pregnancy outcome of wives of a control group made up of unexposed rubber workers and PVC fabricators believed to be exposed to "very low" levels of vinyl chloride (Infante et al. 1976a, 1976b). Pregnancy outcomes were determined based on the responses given by fathers on a questionnaire. Infante et al. (1976a, 1976b) and NIOSH (1977) reported a significant excess of fetal loss in the group whose husbands had been exposed to vinyl chloride. The greatest difference occurred in wives of men under 30 years of age, where fetal loss was 5.3% for controls and 20.0% for exposed workers. However, this study has been severely criticized based on the conduct of the study and method of statistical analysis used (Hatch et al. 1981; Stallones 1987). Furthermore, Hatch et al. (1981) and Stallones (1987) concluded that the study failed to demonstrate an association of parental exposure to vinyl chloride with increased fetal loss.

Additional work by Infante (1976) and Infante et al. (1976b) examined the occurrence of congenital malformations among populations exposed to emissions from PVC polymerization facilities. A statistically significant increase in birth defects was observed in three cities in which polymerization facilities were located when compared to statewide and countywide averages. The greatest increases were noted in malformations of the central nervous system, upper alimentary tract, and genital organs and in the incidence of club foot. However, this study has also been criticized based on the conduct and analyses used (Hatch et al. 1981; Stallones 1987). These authors concluded that the study failed to demonstrate an association between exposure to emissions and the prevalence of birth defects. Furthermore, another study that examined the incidence of malformations in one of the cities studied by Infante (1976) concluded that, although the city had statistically increased incidences of congenital malformations, no correlation existed with parental proximity to the polymerization plant or with parental employment at the plant (Edmonds et al. 1975). In fact, more parents of control infants worked at the plant or lived closer to the plant than parents of infants with central nervous system malformations.

Additional studies have also examined the prevalence of congenital malformations in populations exposed to emissions from polymerization facilities (Edmonds et al. 1978; Rosenman et al. 1989; Theriault et al. 1983). The incidence of central nervous system defects in a West Virginia county with a polymerization plant was compared to incidences in other regions in the United States with no known exposure to vinyl chloride (Edmonds et al. 1978). Although the rate of central nervous system defects in the West Virginia county exceeded that in control areas, no correlation was noted between the increased central nervous system defects and parental occupation or potential exposure based on proximity to the plant or prevailing wind patterns.

A significantly greater prevalence of birth defects was found in residents of a town with a polymerization facility than in three matched towns without potential for exposure to vinyl chloride (Theriault et al. 1983). The most commonly reported defects included those of the musculoskeletal, alimentary, urogenital, and central nervous systems. The incidences were observed to fluctuate with seasonal changes in emissions. However, no correlations were found between the presence of defects and proximity of the residence to the plant or parental occupation. Also, other industrial emissions could not be eliminated as potential sources of the increased incidence of congenital malformations observed and additional confounding factors such as nutritional status, smoking, and alcohol and other drug use were not eliminated.

No significant increases in birth defects were observed in a community with two polymerization facilities, but odds ratios for central nervous system defects were found to correlate with the amount of emissions from the individual facilities and with the distance of the residences of affected parents from the facilities (Rosenman et al. 1989). However, this study was limited by the small sample size.

Pregnancy outcomes of mothers occupationally exposed to vinyl chloride for more than 1 year were compared to those of pregnant workers not exposed to vinyl chloride in retrospective and prospective studies (Bao et al. 1988). Company records indicated that exposure levels ranged from 3.9 to 89.3 ppm during the retrospective study and from 0.2 to 130.7 ppm during the prospective study. More detailed information regarding the exposure levels was not presented. The study authors concluded that exposure to vinyl chloride did not correlate with changes in sex ratio, birth weight or height, perinatal mortality, or the incidence of congenital abnormalities.

A number of inhalation studies have examined the effects of vinyl chloride exposure on pregnancy outcome in animals. Results of these studies indicate that vinyl chloride produces adverse developmental

effects at concentrations that are also toxic to maternal animals. John et al. (1977, 1981) exposed rats and rabbits to 0, 500, or 2,500 ppm and mice to 0, 50, or 500 ppm throughout the period of organogenesis. Separate control groups were used for each of the mice exposure concentrations. Mice were most sensitive to the effects of vinyl chloride. In mice exposed to 500 ppm, maternal toxicity was evidenced by decreased food consumption, decreased body weight gain, and increased mortality rate (John et al. 1977, 1981). Delayed ossification was noted in fetuses at 500 ppm. The only significant fetal effect observed at 50 ppm was an increase in crown-rump length. The biological significance of this effect is unknown. Based on this NOAEL of 50 ppm, an acute-duration MRL of 0.5 ppm was calculated as described in the footnote in Table 3-1. In rats, 500 ppm produced decreased maternal weight gain and fetal weight, increased crown-rump length, and vertebral lumbar spurs. Increasing the exposure level to 2,500 ppm was not associated with a dose-dependent increase in these effects. The only effects observed at 2,500 ppm were decreased maternal food consumption and, in fetuses, an increased incidence of dilated ureters. In rabbits exposed to 500 ppm, maternal animals had decreased food consumption, and fetal animals had delayed ossification. These effects were not observed in rabbits at 2,500 ppm. However, the number of animals that were tested at 2,500 ppm was much lower than at 500 ppm (5 versus 20); thus, no conclusions may be drawn as to the dose response of these effects.

An embryo-fetal developmental toxicity study was conducted in rats exposed to vinyl chloride via inhalation (Thornton et al. 2002). Female Sprague-Dawley rats were exposed to 0, 10, 100, or 1,100 ppm vinyl chloride 6 hours/day on Gd 6–19. No adverse effects were noted in embryo-fetal developmental parameters including uterine implantation, fetal gender distribution, fetal body weight, and fetal malformations and variations. Vinyl chloride produced a decrease in maternal body weight gain at all exposure levels; however, no changes were observed in feed consumption, clinical signs, or postmortem gross findings. Maternal liver and kidney weights were increased relative to total body weight.

Exposure of rats to either 0 or 1,500 ppm of vinyl chloride during the first, second, or third trimester of pregnancy was examined (Ungvary et al. 1978). In maternal animals, an increased liver-to-body- weight ratio was observed in those exposed during the first and second trimesters, but no histopathologic alterations were found. A significant increase in resorptions was observed in animals exposed during the first trimester of pregnancy. Two central nervous system malformations (microphthalmia and anophthalmia) were observed in exposed fetuses but not in controls, but the incidence of these malformations did not reach statistical significance. This study is limited in that only a single concentration of vinyl chloride was tested, precluding conclusions as to the dose-response relationship of the effects observed.

The effects of exposure of rats to vinyl chloride throughout gestation were examined by Mirkova et al. (1978) and Sal'nikova and Kotsovskaya (1980). An unspecified number of pregnant rats were exposed to 0, 1.9, or 13.9 ppm for 4 hours/day for the 21 days of gestation. Fetuses were examined for abnormalities just prior to the end of gestation, and offspring were examined at 6 months postparturition (Sal'nikova and Kotsovskaya 1980). At 13.9 ppm, a decrease in maternal erythrocyte count was observed. At 1.9 and 13.9 ppm, fetuses had an increased incidence of hemorrhages, and at 13.9 ppm, increased edema. However, the affected organs were not specified. Rats examined at 6 months, following *in utero* exposure to 1.9 ppm, were found to have decreased hemoglobin and leukocytes and decreased organ weights (males: liver, kidneys, spleen; females: lung, liver). In addition to these effects, exposure to 13.9 ppm *in utero* resulted in an increased hexanol sleep time and a decreased ability of the rats to orient themselves.

Continuous exposure of an unspecified number of rats throughout gestation to 2.4 ppm of vinyl chloride resulted in decreased fetal weight and increased early postimplantation loss, hematomas, and hydrocephaly with intracerebral hematoma. Weanling rats had hepatotoxic effects including decreased bile enzyme activity, decreased bile secretion, and decreased cholic acid content,. No histological data on the livers of pups, or information regarding maternal health, or statistical analyses of the data were presented (Mirkova et al. 1978). Also, both this study and the report by Sal'nikova and Kotsovskaya (1980) failed to provide information on the number of animals in each test group.

The developmental toxicity of vinyl chloride was examined using a whole embryo culture system (Zhao et al. 1996). Vinyl chloride induced embryo growth retardation, but was not shown to be teratogenic in the rat *in vitro* whole embryo culture system.

The highest NOAEL value and all reliable LOAEL values for developmental effects in mice, rats, and/or rabbits in acute-duration studies are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.7 Cancer

The most compelling evidence for the carcinogenic potential of vinyl chloride in humans comes from the cluster of reports of greater than expected incidences of angiosarcoma of the liver in workers occupationally exposed to vinyl chloride (Byren et al. 1976; Creech and Johnson 1974; Fox and Collier

1977; Infante et al. 1976b; Jones et al. 1988; Laplanche et al. 1992; Lee et al. 1996; Monson et al. 1975; Pirastu et al. 1990; Rinsky et al. 1988; Simonato et al. 1991; Teta et al. 1990; Theriault and Allard 1981; Waxweiler et al. 1976; Weber et al. 1981; Wong et al. 1991; Wu et al. 1989). Angiosarcoma of the liver is considered to be a very rare type of cancer (25–30 cases/year in the United States) (Heath et al. 1975). However, approximately 30 years after the introduction of vinyl chloride for use in the industrial production of PVC, it became apparent that workers exposed to high levels of vinyl chloride had an unusually high incidence of this type of tumor. Investigators identified an increased likelihood of developing hepatic angiosarcoma among those exposed to the highest levels of vinyl chloride and those exposed to vinyl chloride for the longest duration (Fortwengler et al. 1999; Fox and Collier 1977; Infante et al. 1976b; Jones et al. 1988; Rinsky et al. 1988; Weber et al. 1981; Wong et al. 1991; Wu et al. 1989). Angiosarcoma of the liver was not found in residents living in the vicinity of vinyl chloride sites, unless they were also exposed to high concentrations of vinyl chloride in the workplace (Elliott and Kleinschmidt 1997). Based on this information, vinyl chloride is considered to be a carcinogen in humans (EPA 1994c; IARC 1987).

Histopathological examination of liver tissue from humans with hepatic angiosarcoma has led to the hypothesis that angiosarcoma develops as a result of hyperplastic changes in sinusoidal cells. Areas of transition to angiosarcoma contained greatly increased numbers of sinusoidal cells with greatly expanded sinusoidal spaces. Also, hepatic cells were replaced by fibrous tissue forming trabeculae. These areas also showed infiltration of angiosarcoma cells. In fully developed angiosarcoma, multiple areas with nodules of angiosarcoma cells were noted, the centers of which exhibited hemorrhagic necrosis (Popper et al. 1981). A recent case report suggests that vinyl chloride can also produce malignant hemangiopericytoma in the liver, which is a vascular tumor similar to angiosarcoma (Hozo et al. 1997, 2000).

Other liver tumors, including hepatocellular carcinoma and cholangiocellular carcinoma, have also been associated with occupational exposure to vinyl chloride (Cheng et al. 1999; Du and Wang 1998; Lelbach 1996; Saurin et al. 1997; Ward et al. 2001; Weihrauch et al. 2000; Wong et al. 2002a, 2003a). A meta-analysis of eight independent studies confirms an increased risk of hepatocellular carcinoma for occupational workers exposed to vinyl chloride (Boffetta et al. 2003). The risk of developing liver cancer appears elevated in those with a history of Hepatitis B viral infection (Du and Wang 1998; Wong et al. 2003a).

Other cancers that have shown a statistically significant increase in mortality rate among vinyl chloride workers, in at least some studies, include cancer of the brain and central nervous system, the lung and

respiratory tract, connective and other soft tissues, and the lymphatic/hematopoietic system. With regard to cancer of the brain and central nervous system, Cooper (1981), Waxweiler et al. (1976), and Wong et al. (1991) reported statistically significant increases; Monson et al. (1975) reported an increase in central nervous system cancer mortality in a proportional mortality study; Byren et al. (1976), Simonato et al. (1991), and Tabershaw and Gaffey (1974) reported increases that were not statistically significant; and Fox and Collier (1977), Jones et al. (1988), Thomas et al. (1987), and Wu et al. (1989) found no increase in cancer of the central nervous system among workers occupationally exposed to vinyl chloride. It should be noted that the Cooper (1981), Tabershaw and Gaffey (1974), and Wong et al. (1991) studies were all based on the same cohort from a Chemical Manufacturers Association (CMA) study (Wong and Whorton 1993). Workers in the studies by Waxweiler et al. (1976) and Wu et al. (1989) were also employed at the same plants used for the CMA study (Wong and Whorton 1993). At least one analysis of epidemiological studies exposed certain weaknesses in the data that support a causal link between vinyl chloride and brain cancer (Doll 1988).

Follow up mortality studies at polymer production plants indicate that liver cancer mortality remained elevated while brain cancer mortality was markedly reduced (as compared to earlier studies). It should be noted that increased brain cancer incidence was not associated with vinyl chloride exposure in these later studies (Lewis 2001; Lewis and Rempala 2003; Lewis et al. 2003; Mundt et al. 2000). In a meta-analysis of eight independent studies, no statistically significant increase in brain cancer mortality was observed (Boffetta et al. 2003). An IARC update of a European multi-center cohort study was also negative for brain cancer (Ward et al. 2001).

An association between respiratory tract cancer and vinyl chloride exposure has not been consistently observed. A significant increase in cancer of the respiratory tract was reported by Belli et al. (1987), Infante et al. (1976b), and Waxweiler et al. (1976), and also by Monson et al. (1975) in a proportional mortality study. Although smoking history was not considered in these studies, Waxweiler et al. (1976) noted that the types of respiratory tract cancer most frequently recorded were large-cell undifferentiated carcinoma or adenocarcinoma, which are two lung cancer types not usually associated with smoking, but may be due to concomitant exposure. Increased risk of lung cancer was also associated with exposure to high concentrations of polyvinyl chloride dust particles (Mastrangelo et al. 2002). Respiratory tract cancer was not reported as elevated in studies by Cheng et al. (1999), Cooper (1981), Fox and Collier (1977), Jones et al. (1988), Mundt et al. (2000), Simonato et al. (1991), Wong et al. (1991, 2002a), and Wu et al. (1989). Similarly, a meta-analysis of eight independent studies (Boffetta et al. 2003) and an

IARC update of a multi-center cohort study did not demonstrate excess mortality from lung cancer (Ward et al. 2001).

A significant increase in cancers of connective and other soft tissues was observed in a recent follow up mortality study (Mundt et al. 2000) and in a meta-analysis of eight independent studies (Boffetta et al. 2003). Rhomberg (1998) also suggests that vinyl chloride can induce soft tissue sarcoma outside of the liver; however, an IARC update of a multi-center cohort study was negative for soft tissue sarcoma (Ward et al. 2001). A meta-analysis of five occupational exposure studies additionally suggests a weak association between vinyl chloride exposure and pancreatic cancer (Ojajarvi et al. 2001).

A statistically significant increase in cancers of the lymphatic/hematopoietic system was reported by Rinsky et al. (1988), Smulevich et al. (1988), Weber et al. (1981), and Wong et al. (2002a). Monson et al. (1975) also reported an increase in their proportional mortality study. However, no statistically significant increase in these types of cancer was reported by Infante et al. (1976b), Jones et al. (1988), Mundt et al. (2000), or Wong et al. (1991). In a meta-analysis of eight independent studies, the mortality data for cancers of the lymphatic/hematopoietic system were highly variable. A strong association was not observed between vinyl chloride exposure and lymphatic/hematopoietic system cancers; however, a negative conclusion was considered premature (Boffetta et al. 2003).

An increased incidence of malignant melanoma among vinyl chloride workers has been reported (Heldaas et al. 1984, 1987), but the significance of this finding has been disputed (ten Berge 1987). A follow up to the original Heldaas (1984, 1987) studies reported only one additional case of melanoma between 1985 and 1993, weakening the proposed association between vinyl chloride exposure and the development of malignant melanoma (Langard et al. 2000).

A recent review pooled the analyses of worker cohort from 56 vinyl chloride plants in North America and Europe (Bosetti et al. 2003). This analysis includes over 22,000 workers and represents the most comprehensive data on occupational risks of vinyl chloride exposure. An elevated risk of liver cancer mortality was observed. Deaths from lung and laryngeal cancer were lower than expected and no excess cancer risk was observed for soft tissue sarcoma or brain, lymphoid, and hematopoietic system cancers. Lewis (1999) reports the continuing occurrence of angiosarcoma of the liver in retirees from a PVC production plant in Louisville, Kentucky. This ongoing incidence is reported primarily for those workers employed prior to 1960, suggesting that those exposed to the highest concentrations of vinyl chloride remain at risk for developing cancer for the remainder of their lives. The reported latency period for

workers diagnosed prior to 1975 was 12–28 years, while those diagnosed after 1975 showed a latency of 27–47 years.

Few studies directly address the incidence of cancer in women occupationally exposed to vinyl chloride. However, one study found that women employed in the production of vinyl chloride and PVC had a significantly greater chance of developing leukemia or lymphomas (Smulevich et al. 1988). Furthermore, the subgroup of women who were exposed to the highest levels of vinyl chloride had increased incidences of stomach cancer and the highest incidences of leukemia and lymphoma. No significant increase in any type of cancer was observed in exposed males in this report, irrespective of the level of exposure.

Studies in several animal species support the conclusion that vinyl chloride is carcinogenic. A large series of experiments was performed by Maltoni et al. (1981) using rats (Sprague-Dawley and Wistar), mice, and hamsters. All animals were chamber exposed; controls were chamber exposed to air only. The test material was >99.9% pure. A complete gross and histopathological examination of every animal was performed. However, extremely limited histopathological data were presented and cancer incidences were presented only in summary tables. Also, survival of control animals was poor in some of the experiments. Furthermore, statistical analyses, where present, appear to be based on a compilation of data from several individual studies. In one group of studies, Maltoni et al. (1981) exposed Sprague-Dawley rats to vinyl chloride for 52 weeks at concentrations ranging from 1 to 30,000 ppm. Animals were examined at the time of their spontaneous death. Statistically significant increases were noted in the incidence of mammary gland carcinomas, Zymbal gland carcinomas, nephroblastoma, and liver angiosarcoma. Exposure of Swiss mice to 50 ppm vinyl chloride for 4 hours/day, 5 days/week for 30 weeks also appeared to increase the incidence of liver angiosarcoma and angioma (Maltoni et al. 1981). Maltoni et al. (1981) also reported that decreasing the duration of exposure decreased the incidence of vinyl chloride-related tumors (nephroblastomas, liver angiosarcomas, Zymbal gland carcinomas, and to some extent, neuroblastomas), but statistics were not presented to support these conclusions.

Some variation in the target organs that developed tumors was observed when different species were exposed to vinyl chloride (Maltoni et al. 1981). Whereas angiosarcomas of the liver were reported to occur in rats, mice, and hamsters, mammary gland carcinomas were found only in rats and mice; Zymbal gland carcinomas, neuroblastomas, and nephroblastomas were found only in rats; lung tumors were found only in mice; and melanomas, acoustical duct epithelial tumors, and leukemias were found only in hamsters.

Other inhalation experiments support the carcinogenicity of vinyl chloride. Rats and mice exposed to 0, 50, 250, or 1,000 ppm for 6 hours/day, 5 days/week for 6 months (Hong et al. 1981) or up to 12 months (Lee et al. 1977a, 1978) had a significantly increased incidence of hemangiosarcoma of the liver at ≥250 ppm. Increases in bronchio-alveolar adenoma of the lung and mammary gland tumors (adenocarcinomas, squamous and anaplastic cell carcinomas) were also observed in mice at ≥50 ppm, although it is unclear whether the increases in these tumor types are statistically significant (Lee et al. 1977a, 1978). Male rats exposed to concentrations as low as 100 ppm for 6 hours/day, 6 days/week, for 12 months had significantly increased incidence of cancer, including angiosarcoma of the liver and lung, when sacrificed at 18 months (Bi et al. 1985). Rats exposed to 30,000 ppm vinyl chloride 4 hours/day, 5 days/week, for 12 months had an increased incidence of epidermoid carcinoma of the skin, adenocarcinoma of the lungs, and osteochondroma in the bones (Viola et al. 1971), and rats exposed to 5,000 ppm for 52 weeks had primary tumors in the brain, lung, Zymbal gland, and nasal cavity (Feron and Kroes 1979). However, these studies (Feron and Kroes 1979; Viola et al. 1971) are limited by the absence of statistical analysis of the data. A concentration-dependent increase in tumor formation (alveologenic adenomas of the lung, angiosarcomas of the liver, and adenosquamous carcinoma of the mammary gland) was observed in mice exposed to 0, 50, 200, or 2,500 ppm vinyl chloride in a study performed for the Manufacturing Chemists Association (Keplinger et al. 1975). However, no statistics were presented to support these conclusions. Furthermore, an audit of data performed for the Manufacturing Chemists Association (CMA 1979) indicated that mishandling of the tissues precluded making statements regarding the relationship of tumors other than angiosarcoma of the liver to vinyl chloride exposure. Female mice exposed to 50 ppm vinyl chloride showed increased incidence of hemangiosarcoma of the subcutis and peritoneum as well as tumors of the lung and mammary gland (Drew et al. 1983), i.e., hemangiosarcoma of the skin, spleen, or liver and mammary gland carcinomas.

In a preliminary study with a limited number of animals, alveogenic lung tumors developed in 26 of 27 mice exposed to 2,500 or 6,000 ppm for 5–6 months (Suzuki 1978). A concentration-related increase in the incidence of alveogenic tumors was observed in a study in which a greater number of mice were exposed to 0–600 ppm for 4 weeks and then observed for up to 40 weeks postexposure (Suzuki 1983). The lowest concentration at which multiple foci tumors were observed was 100 ppm (Suzuki 1983.) A significant increase in the incidence of pulmonary adenomas was reported in mice exposed to 50 ppm, 6 hours/day, 5 days/week for 6 months (Adkins et al. 1986). An increase in bronchio-alveolar adenoma was observed in a lifespan study in mice that were exposed to 50 ppm for 100 1-hour exposures, 500 ppm

for 10 1-hour exposures, or 5,000 ppm for a single 1-hour exposure (Hehir et al. 1981). The statistical significance of these observations was not presented.

Some data suggest that exposure of animals early in their lives may increase the likelihood of developing tumors due to the latency period for vinyl chloride-induced cancer (Drew et al. 1983). Early life exposure may also affect the type of tumor that develops (Maltoni et al. 1981). When hamsters, mice, and rats were exposed to vinyl chloride for periods of 6–24 months starting at various times after weaning, the incidence of tumors such as hemangiosarcoma of the liver, skin, and spleen, and angiosarcoma of the stomach was greater when animals were exposed for 12 months immediately after weaning than if animals were held for 12 months and then exposed for the next 12 months (Drew et al. 1983). Mammary gland carcinoma was also significantly increased when 2- or 8-month-old hamsters, but not 14- or 20-month-old hamsters, were exposed to 200 ppm vinyl chloride for 6 months (Drew et al. 1983). Fibroadenoma of the mammary gland was also increased in female rats exposed to 100 ppm of vinyl chloride for 6 hours/day, 5 days/week, over 6–24 months (Drew et al. 1983). Also, when pregnant rats were exposed to 6,000 ppm vinyl chloride from gestation day 12 through 18, the incidence of mammary gland carcinomas, Zymbal gland carcinomas, and forestomach epithelial tumors was reported to be greater in transplacentally exposed animals than in maternal animals (Maltoni et al. 1981). At 10,000 ppm in this study, nephroblastomas were increased in transplacentally exposed animals compared to maternal animals (Maltoni et al. 1981). No control group was used, however, and no statistics were presented to support the conclusions. Maltoni and Cotti (1988) also exposed pregnant rats to 2,500 ppm vinyl chloride starting on Gd 12 and continued to expose both maternal animals and offspring for a total of 76 weeks. Hepatocarcinoma, hepatic angiosarcoma, and neuroblastoma were increased in treated animals compared to controls. The incidence of hepatocarcinoma was reported to be much higher in offspring than in maternal animals. In contrast, the incidence and latency period of neuroblastomas and hepatic angiosarcomas was similar between offspring and parents. However, no statistics were presented to support these conclusions.

Many of the tumors that were observed in the Drew et al. (1983) and Maltoni et al. (1981) studies were also observed in a study performed by Froment et al. (1994). In this study, Sprague-Dawley pups were exposed to 500 ppm vinyl chloride 8 hours/day, 6 days/week, on postpartum days 3–28. After weaning, 22 animals/gender were exposed for an additional 2 weeks, for a total exposure duration of 33 days. Rats were observed daily until death or development of tumors, and the surviving rats were sacrificed at 19 months. All livers from exposed animals that appeared normal at gross examination were found to contain multiple nodular hyperplastic foci of hepatocytes. Liver tumors that were found in exposed

animals included angiosarcomas, hepatocellar carcinomas, and benign cholangiomas. Other tumors found included pulmonary angiosarcoma (probably metastatic), nephroblastoma, abdominal angiomyoma, leukemia, Zymbal gland carcinoma, pituitary adenoma, mammary carcinoma, and mammary fibroma. Tumor incidence was not reported in control animals. Only one concentration (500 ppm) of vinyl chloride was used because the purpose of the study was to examine the genotoxicity of vinyl chloride in liver tumors produced by exposure.

In general, the available evidence from inhalation studies in animals supports the finding in humans; that vinyl chloride is a carcinogen by this route of exposure. Based on these and other findings, the National Toxicology Program of the Department of Health and Human Services has determined vinyl chloride to be a known human carcinogen (DHHS 2002). In addition, IARC has concluded that sufficient evidence for carcinogenicity in humans and animals exists and has placed vinyl chloride in carcinogenicity category 1 (i.e., carcinogenic to humans) (IARC 1987). EPA also has concluded that sufficient evidence of carcinogenicity exists in humans and animals and has classified vinyl chloride according to its 1986 classification scheme as a Group A or known human carcinogen (EPA 1994c). EPA's current weight-of-evidence characterization for vinyl chloride concludes that vinyl chloride is a *known human carcinogen by the inhalation route of exposure*, based on human epidemiological data. By analogy, vinyl chloride is *carcinogenic by the oral route* because of positive animal bioassay data as well as pharmacokinetic data allowing dose extrapolation across routes. Vinyl chloride is also considered highly *likely to be carcinogenic by the dermal route* because it is well absorbed and acts systemically (EPA 2000). Because the epidemiological evidence does not provide sufficient exposure and incidence data to quantify risk based solely on human data, EPA cancer potency factors for inhalation and oral exposure have been calculated based on animal studies. An inhalation unit risk of 8.8×10^{-6} per ug/m^3 for continuous lifetime exposure from birth was estimated by EPA (2000) based on the incidence of liver tumors observed in rats in the inhalation study by Maltoni et al. (1981). An inhalation unit risk of 4.4×10^{-6} per ug/m^3 for continuous lifetime exposure during adulthood was also estimated by EPA (2000). Air concentrations associated with excess cancer risks of 10^{-4}, 10^{-5}, and 10^{-6} by are plotted in Figure 3-1. These risks were calculated using physiologically based pharmacokinetic (PBPK) modeling, which is discussed in further detail in Section 3.4. The lowest concentrations tested that produced a tumorigenic response CEL for each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2 Oral Exposure

All dosages of vinyl chloride administered in the diet are reported as mg/kg (body weight)/day unless otherwise specified.

3.2.2.1 Death

No studies were located regarding lethal effects in humans following oral exposure to vinyl chloride.

No studies were located regarding acute or intermediate lethal effects of vinyl chloride in animals. However, decreased longevity has been observed in rats as a result of chronic ingestion of vinyl chloride. Significant increases in mortality were observed by Feron et al. (1981) when Wistar rats were allowed to consume vinyl chloride doses as low as 5.6 mg/kg/day in the diet for 4 hours/day over a 2-year period. Also, the effects of consumption of vinyl chloride during a lifespan study in Wistar rats lasting almost 3 years (149 weeks) were examined by Til et al. (1983, 1991). These authors found a decreased survival rate at a vinyl chloride dosage of 1.7 mg/kg/day. In both of these studies, vinyl chloride was administered by incorporating PVC resin that was high in vinyl chloride content into the diet. In the Til et al. (1991) study, the diets of the control animals contained 1% PVC powder that did not contain residual vinyl chloride. Vaporization of vinyl chloride from the diets was limited by presenting feed containing the vinyl chloride to the rats for only a 4-hour period.

All reliable LOAEL values for death in rats following chronic exposure are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for hematological, hepatic, dermal, and body weight effects in rats following chronic oral exposure are recorded in Table 3-2 and plotted in Figure 3-2.

No studies were located regarding adverse respiratory, cardiovascular, gastrointestinal, musculoskeletal, renal, endocrine, or ocular effects in humans or animals following oral exposure to vinyl chloride.

Table 3-2 Levels of Significant Exposure to Vinyl Chloride - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Death						
1	Rat (Wistar)	2 yr 5 d/wk 4 hr/d (F)				5.6 (100% died)	Feron et al. 1981
2	Rat (Wistar)	149 wk 4 hr/d (F)				1.7 (increased mortality)	Til et al. 1983, 1991
	Systemic						
3	Rat (Wistar)	2 yr 5 d/wk 4 hr/d (F)	Hemato	5.6	17 (decreased clotting time)		Feron et al. 1981
			Hepatic		1.8 (cellular alteration)	17 M extensive necrosis	
						5.6[b] F (extensive necrosis)	
4	Rat (Wistar)	2 yr 1 x/d (GO)	Dermal		30 (increased skin thickness, collagen)		Knight and Gibbons 1987

Table 3-2 Levels of Significant Exposure to Vinyl Chloride - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
5	Rat (Wistar)	149 wk 4 hr/d (F)	Hemato	1.7			Til et al. 1983, 1991
			Hepatic	0.17[c] F	1.7 F (liver cell polymorphism)		
			Bd Wt	1.7			
	Cancer						
6	Rat (Wistar)	2 yr 5 d/wk 4 hr/d (F), (GO)				5.6 M (CEL: angiosarcoma of lung; neoplastic nodules of liver, hepatic angiosarcoma) 1.8[b] F (CEL: neoplastic nodules of liver)	Feron et al. 1981
7	Rat (Sprague-Dawley)	52 wk 5 x/wk (GO)				50 M (CEL: liver angiosarcoma) 16.65[b] F (CEL: liver angiosarcoma)	Maltoni et al. 1981
8	Rat (Sprague-Dawley)	52 wk 5 x/wk (GO)				0.3 (CEL: liver angiosarcoma, hepatoma)	Maltoni et al. 1981

Table 3-2 Levels of Significant Exposure to Vinyl Chloride - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
9	Rat (Wistar)	149 wk 4 hr/d (F)				1.7 M	(CEL: hepatocellular carcinoma)	Til et al. 1983, 1991
						1.7 F	(CEL: neoplastic nodules of liver)	
						0.018[b] F	(CEL: basophilic foci considered to be pre-neoplastic lesions)	
						1.7	(CEL: hepatic angiosarcoma)	

a Numbers correspond to entries in Figure 3-2.

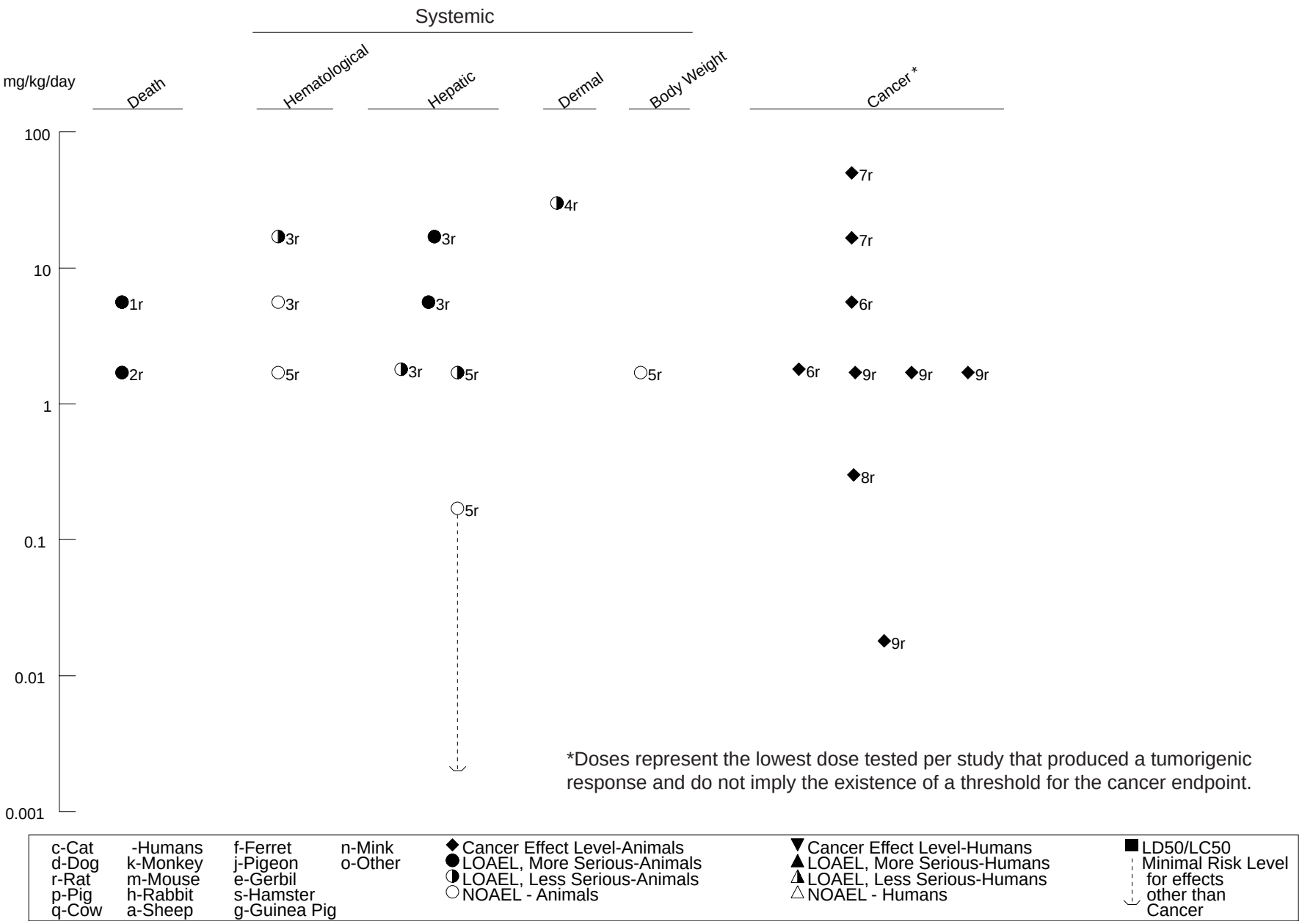
b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c Used to derive an chronic-duration Minimal Risk Level (MRL) of 0.002 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

B - both; Bd Wt = body weight; CEL = cancer effect level; d = day(s); derm = dermal; (F) = feed; F = Female; (GO) = gavage in oil; hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; wk = week(s); x = time(s); yr = year(s)

Figure 3-2. Levels of Significant Exposure to Vinyl Chloride- Oral

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

Hematological Effects. No studies were located regarding adverse hematological effects in humans after oral exposure to vinyl chloride.

Rats fed 17 mg/kg/day for 2 years showed decreased clotting time of the blood, which was not observed at 5.6 mg/kg/day (Feron et al. 1981). No changes in thrombocyte count or prothrombin times were noted in Wistar rats fed diets containing low concentrations of vinyl chloride in PVC resin (1.7 mg/kg/day) for 149 weeks (Til et al. 1983, 1991).

Hepatic Effects. No studies were located regarding adverse hepatic effects in humans after oral exposure to vinyl chloride.

Chronic exposure of rats to vinyl chloride in their feed for 149 weeks produced an increase in the incidence of several types of microscopic liver lesions in male and female rats. Neoplastic and preneoplastic lesions in the liver included several types of foci of cellular alteration (i.e., clear-cell, basophilic, eosinophilic, or mixed), neoplastic nodules, hepatocellular carcinoma, and angiosarcoma. Other liver lesions associated with vinyl chloride exposure included liver-cell polymorphism and hepatic cysts. The high-dose group in male and female rats (1.7 mg/kg/day) represents a LOAEL for noncancer liver effects in this study (i.e, liver cell polymorphism, hepatic cysts) (Til et al. 1983, 1991). The human equivalent NOAEL dose derived from this study was used as the basis for a chronic oral MRL of 0.003 mg/kg/day. Chronic oral exposure of rats fed vinyl chloride daily during a 4-hour period for 2 years also resulted in areas of hepatocellular alteration at concentrations as low as 1.8 mg/kg/day (Feron et al. 1981). In this study, areas of necrosis were observed in the liver of female rats fed 5.6 mg/kg/day and male rats fed 17 mg/kg/day (Feron et al. 1981). Increased incidence of hepatic cysts were found in female rats fed 1.7 mg/kg/day and clear or basophilic areas of cellular alteration were found in male rats fed 1.7 mg/kg/day in the Til et al. (1983, 1991) studies.

Dermal Effects. No studies were located regarding adverse dermal effects in humans after oral exposure to vinyl chloride.

Daily administration of 30 mg/kg of vinyl chloride to rats by gavage for 2 years produced increased thickness, moisture content, and collagen content of the skin. Newly synthesized intermolecular and intramolecular collagen crosslinks were also significantly increased (Knight and Gibbons 1987).

Body Weight Effects. No studies were located regarding adverse body weight effects in humans after oral exposure to vinyl chloride.

No changes in body weight were noted in Wistar rats fed 1.7 mg/kg/day vinyl chloride mixed with PVC powder in the diet for 149 weeks (Til et al. 1983, 1991).

No studies were located regarding the following health effects in humans or animals after oral exposure to vinyl chloride:

3.2.2.3 Immunological and Lymphoreticular Effects

3.2.2.4 Neurological Effects

3.2.2.5 Reproductive Effects

3.2.2.6 Developmental Effects

3.2.2.7 Cancer

No studies were located regarding cancer in humans following oral exposure to vinyl chloride.

Four studies were located that examined the carcinogenic potential of vinyl chloride in animals when administered by the oral route. In two of these studies, conducted for 149 weeks, vinyl chloride was added to the diet by incorporating PVC powder containing a high level of the monomer (Feron et al. 1981; Til et al. 1983, 1991). To limit volatilization of vinyl chloride from the diet, the rats were allowed access to the diet for only 4 hours/day. The actual intake of vinyl chloride in these reports was calculated by taking into consideration both the food consumption and the rate of vinyl chloride evaporation. Statistically significant increases in hepatic angiosarcoma of the liver were observed in the 2-year study by Feron et al. (1981) at 5.6 mg/kg/day in males and 17 mg/kg/day in females. In the same study, statistically significant increases in neoplastic nodules of the liver were also observed at a concentration of 5.6 mg/kg/day in males but as low as 1.8 mg/kg/day in females (Feron et al. 1981). Also, in the 149-week study by Til et al. (1983, 1991), statistically significant increases in hepatocellular carcinoma were observed in males at 1.7 mg/kg/day and hepatic neoplastic nodules in females at 1.7 mg/kg/day. A few animals exposed to 1.7 mg/kg/day in this study developed hepatic angiosarcoma. An increased

incidence of Zymbal gland tumors was also observed in the study by Feron et al. (1981). Although the increase was not statistically significant, the tumors were considered to be treatment related based on the historical rarity of this type of tumor.

Two studies were located in which vinyl chloride was administered to Sprague-Dawley rats by gavage for 52 weeks. In one of these studies, a statistically significant increase in the incidence of hepatic angiosarcomas was observed at doses as low as 16.65 mg/kg/day in females and 50 mg/kg/day in males. Zymbal gland tumors at 16.65 and 50 mg/kg/day, even though not statistically significant, were considered to be treatment related because of the rarity of this type of tumor (Maltoni et al. 1981). Lower doses of vinyl chloride were also tested in a similar study in which hepatic angiosarcomas were observed at doses as low as 0.3 mg/kg/day and Zymbal gland tumors at 1 mg/kg/day. Although neither of these findings reached statistical significance, the tumors were considered to be treatment related because of the historically rare observation of these tumor types in the colony (Maltoni et al. 1981).

Based on the evidence of carcinogenicity in animals after oral exposure, it would be prudent to consider the potential for carcinogenic effects in humans by this route as well. The National Toxicology Program of the Department of Health and Human Services has determined vinyl chloride to be a known human carcinogen (DHHS 2002). In addition, IARC has concluded that sufficient evidence for carcinogenicity in humans and animals exists and has placed vinyl chloride in carcinogenicity category 1 (i.e., carcinogenic to humans) (IARC 1987). EPA also has concluded that sufficient evidence of carcinogenicity exists in humans and animals and has classified vinyl chloride according to its 1986 classification scheme as a Group A or known human carcinogen (EPA 1994c). EPA's current weight-of-evidence characterization for vinyl chloride concludes that vinyl chloride is a *known human carcinogen by the inhalation route of exposure*, based on human epidemiological data. By analogy, vinyl chloride is considered *carcinogenic by the oral route* because of positive animal bioassay data as well as pharmacokinetic data allowing dose extrapolation across routes. By inference, vinyl chloride is also considered highly *likely to be carcinogenic by the dermal route* because it acts systemically (EPA 2000). Because the epidemiological evidence does not provide sufficient exposure and incidence data to quantify risk based solely on human data, EPA cancer potency factors for inhalation and oral exposure have been calculated based on animal studies. An oral slope factor for continuous lifetime exposure from birth was estimated by EPA (2000) to be 1.5 per mg/kg/day based on the incidence of liver tumors in rats in the study by Feron et al. (1981). An oral slope factor of 7.5×10^{-1} per mg/kg/day for continuous lifetime exposure during adulthood was also estimated by EPA (2000). Oral doses associated with excess cancer risks of 10^{-4}, 10^{-5}, and 10^{-6} are plotted in Figure 3-2. These risks were calculated using PBPK modeling,

which is discussed in further detail in Section 3.4. The lowest doses tested that produced a tumorigenic response (CEL) in rats chronically exposed to vinyl chloride by the oral route are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.3 Dermal Exposure

Dermal exposure to vinyl chloride may occur by skin contact with either gaseous or liquid vinyl chloride. Negligible amounts of gaseous vinyl chloride are absorbed through the skin (see also Section 3.4 regarding absorption by the dermal route). However, dermal exposure can also occur by direct contact of gaseous vinyl chloride with the eyes. Only studies that specifically relate to dermal contact of liquid vinyl chloride or adverse ocular effects occurring with inhalation exposure to gaseous vinyl chloride are discussed below.

3.2.3.1 Death

No studies were located regarding lethal effects in humans or animals after dermal exposure to vinyl chloride.

3.2.3.2 Systemic Effects

No studies were located regarding adverse respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or endocrine effects in humans or animals after dermal exposure to vinyl chloride.

Dermal Effects. Vinyl chloride exists as a liquid when stored under pressure. However, when it is released from pressurized containers, it rapidly vaporizes into gas. Thus, the adverse dermal effects observed after exposure to vinyl chloride are not unique to vinyl chloride but can be expected as a result of a rapidly evaporating liquid on the skin. The effects are due to tissue freezing rather than direct toxicity of vinyl chloride. A man who had liquid vinyl chloride sprayed on his hands developed second degree burns. At first, the man reported that his hands felt numb. Within a short period, the hands had developed marked erythema and edema (Harris 1953).

No studies were located regarding adverse dermal effects in animals after dermal exposure to vinyl chloride.

Ocular Effects. Local burns on the conjunctiva and cornea were observed in a man who died after exposure to an unknown quantity of vinyl chloride escaping from an open valve (Danziger 1960).

No adverse ocular effects were noted in guinea pigs exposed for 30 minutes to up to 400,000 ppm vinyl chloride in inhalation chambers (Mastromatteo et al. 1960).

3.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding adverse immunological and lymphoreticular effects in humans or animals following dermal exposure to vinyl chloride.

3.2.3.4 Neurological Effects

A man who had liquid vinyl chloride sprayed on his hands initially reported that his hands felt numb (Harris 1953).

No studies were located regarding adverse neurological effects in animals after dermal exposure to vinyl chloride.

No studies were located regarding the following adverse health effects in humans or animals after dermal exposure to vinyl chloride:

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.3 GENOTOXICITY

Vinyl chloride has been shown to be mutagenic and clastogenic in both *in vivo* and *in vitro* test systems. Tables 3-3 and 3-4 list the key *in vivo* and *in vitro* genotoxicity studies for vinyl chloride.

Genotoxicity studies of vinyl chloride in humans include a large number of assays for chromosomal aberrations in the cultured lymphocytes of occupationally exposed workers. Studies completed through the mid-1980s generally found a statistically significant increase in the frequency of chromosomal aberrations, usually of the chromatid type (i.e., affecting only one of the two strands formed upon deoxyribonucleic acid [DNA] replication), but also including some chromosomal-type defects such as inversions, rings, and translocations, which affect the entire chromosome (Anderson 1999, 2000). An increase in chromosomal aberrations was also observed following an accidental environmental exposure to vinyl chloride (Becker et al. 2001; Huttner and Nikolova 1998; Huttner et al. 1998, 1999). Workers exposed to vinyl chloride for an average of 15 years were shown to have elevated levels of micronuclei and chromosomal aberrations when compared to the unexposed controls (Garaj-Vrhovac et al. 1990). An increase in chromosome aberrations and micronuclei was correlated with the air concentration of vinyl chloride at a plastics plant and the excretion of thiodyglycolic acid in the urine of exposed workers (Vaglenov et al. 1999). Micronuclei counts were also increased in a group of 52 workers exposed to vinyl chloride levels of 1.3–16.7 ppm compared to those of controls, but these increases were not observed in workers exposed to 0.3–7.3 ppm (Sinues et al. 1991).

Increased sister chromatid exchanges have also been reported in occupationally exposed workers (Fucic et al. 1992, 1995; Kucerova et al. 1979; Sinues et al. 1991; Zhao et al. 1996). Sister chromatid exchange frequencies were significantly increased compared to those of the controls at 0.003–7.3 ppm vinyl chloride (Sinues et al. 1991). A positive correlation between frequency of chromosomal aberrations and length of exposure and history of exposure to excursion levels (up to 2,000 ppm) was reported by Purchase et al. (1978), who examined a cohort of 57 vinyl chloride workers, 19 on-site controls, and five off-site controls. The exposures for this cohort ranged from 1,000 ppm between 1945 and 1955 to 5 ppm since 1975. These authors also reported an effect on chromosomal aberrations from smoking. Smoking and the presence of an aldehyde dehydrogenase 2 genotype was associated with an increase in the frequency of sister chromatid exchange in vinyl chloride workers (Wong et al. 1998). DNA damage in lymphocytes of plastic industry workers was also demonstrated by a single-cell gel electrophoresis technique. A correlation was observed between the severity of DNA damage and the duration of exposure (Awara et al. 1998). DNA single strand breaks present in human lymphocytes from exposed

Table 3-3. Genotoxicity of Vinyl Chloride *In Vivo*

Species (test system)	End point	Results	Reference
Mouse	Dominant lethal	–	Anderson et al. 1976
Rat	Dominant lethal	–	Short et al. 1977
		–	Anderson et al. 1976
		–	Purchase et al. 1975
	Chromosomal aberration	+	Anderson and Richardson 1981
Human lymphocyte	Sister chromatid exchange	–	Hansteen et al. 1978
		+	Kucerova et al. 1979
		+	Sinués et al. 1991
		+	Fucic et al. 1992
		+	Fucic et al. 1995
		+	Fucic et al. 1996a
		+	Fucic et al. 1996b
		+	Zhao et al. 1994
	DNA damage	+	Awara et al. 1998
		+	Du et al. 1995
	Micronuclei	+	Garaj-Vrhovac et al. 1990
		+	Sinués et al. 1991
		+	Vaglenov et al. 1999
	Chromosomal aberration	+	Hansteen et al. 1978
		+	Kucerova et al. 1979
		+	Purchase et al. 1978
		+	Ducatman et al. 1975
		+	Anderson 1980
		+	Fucic et al. 1990
		+	Fucic et al. 1995
		+	Fucic et al. 1996a
		+	Fucic et al. 1996b
		+	Funes-Cravioto et al. 1975
		+	Hrivnak et al. 1990
		+	Garaj-Vrhovac et al. 1990
		+	Anderson, 1999
		+	Becker et al. 2001
		+	Huttner et al. 1998

Table 3-3. Genotoxicity of Vinyl Chloride *In Vivo*

Species (test system)	End point	Results	Reference
Human lymphocyte *(cont.)*	Chromosomal aberration	+	Huttner et al. 1999
		+	Huttner and Nikolova 1998
		+	Fucic et al. 1992
		+	Vaglenov et al. 1999
Rat	DNA alkylation	+	Laib et al. 1989
		+	Green and Hathaway 1978
		+	Gwinner et al. 1983
		+	Singer et al. 1987
		+	Bolt et al. 1986
		+	Ciroussel et al. 1990
		+	Eberle et al. 1989
Mouse	DNA alkylation	+	Osterman-Golkar et al. 1977
	DNA damage	+	Walles et al. 1988
Rat	DNA adduct	+	Fedtke et al. 1990
		+	Ciroussel et al. 1990
		+	Swenberg et al. 1992
		+	Bolt et al. 1986
		+	Morinello et al. 2002a, 2002b
		+	Eberle et al. 1989

– = negative result; + = positive result; DNA = deoxyribonucleic acid

Table 3-4. Genotoxicity of Vinyl Chloride *In Vitro*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Salmonella typhimurium	Reverse mutation	+	–	Rannug et al. 1974
		+	+	Bartsch et al. 1975, 1976
		+	+	Andrews et al. 1976
		+	+	Simmon et al. 1977
		Not tested	–	Elmore et al. 1976
		+	+	Poncelet et al. 1980
		+	+	De Meester et al. 1980
		+	+	Victorin and Stahlberg 1988a
		+	Not tested	McCann et al. 1975
		+	+	Rannug et al. 1976
TA100, TA1535	Base-pair substitution	+	+	duPont 1992a, 1992b
TA98, TA1537, TA1538	Frameshift mutation	–	–	
Escherichia coli		Not applicable	+	Jacobsen et al. 1989
Saccharomyces cerevisiae		Not tested	–	Shahin 1976
Schizosaccharomyces pombe	Forward mutation	+	–	Loprieno et al. 1977
Chinese hamster ovary cells		Not applicable	+	Huberman et al. 1975
		+	–	duPont 1992c
Bacillus subtilis	Rec-repair	Not tested	–	Elmore et al. 1976
Rat liver microsomes	RNA alkylation	Not applicable	+	Laib and Bolt 1977
QT6 (avian cells)	Inhibition of DNA synthesis	Not applicable	+	Kandala et al. 1990

+ = positive result; – = negative result; DNA = deoxyribonucleic acid; RNA = ribonucleic acid

workers were quickly repaired following cessation of exposure (Du et al. 1995). Induction of single-strand breaks in liver DNA was also observed in mice after inhalation of vinyl chloride (Walles et al. 1988).

The reversibility of chromosome damage has been reported for several populations of workers following a cessation or reduction of exposure to vinyl chloride. The increase of chromosome aberrations observed in workers exposed to 50 ppm returned to normal within 42 months after exposure levels had been reduced to <5 ppm (Anderson et al. 1980). Another study demonstrated a statistically significant increase in aberrations in workers exposed to concentrations of approximately 25 ppm. Following a reduction in exposure to 1 ppm, vinyl chloride chromosomal aberrations had returned to control values (Hansteen et al. 1978). A 9-year follow-up study of an occupationally exposed population demonstrated a decrease in chromosome aberrations and sister chromatid exchange frequencies over time, corresponding to a decrease in vinyl chloride air concentrations at the plant (Fucic et al. 1996a, 1996b).

The reversibility of clastogenic effects was not seen in another study of 12 current and 3 retired plastics industry workers who had been exposed to vinyl chloride while employed for 1.5–35 years (Fucic et al. 1992). Sister chromatid exchange frequencies were significantly higher in workers exposed to concentrations up to 2,000 ppm than in the controls. These findings showed no significant decrease in sister chromatid exchange frequencies from 8 days to 10 years after exposure (Fucic et al. 1992).

Other papers on human subjects have focused on specific mechanisms involved in the clastogenic effects of vinyl chloride. A cohort of 67 workers exposed to approximately 5 ppm for an average of 15 years was reported to have a nonrandom distribution of chromatid and bichromatid breaks (Fucic et al. 1990). The most frequently affected areas of the genome were the terminal segments of the A, B, and C group chromosomes, suggesting that vinyl chloride or its metabolites interact more frequently with specific sites along the chromosome than would be expected. The study authors presented no correlation with particular fragile sites (gene sequences more prone to breakage than normal) or oncogene locations known to occur at these terminal segments. The implication is that the carcinogenicity of vinyl chloride could be at least partially explained by its nonrandom interaction with particular genes. These workers were also periodically exposed to 2,000 ppm for short periods. No specific information was given as to the frequency or duration of these events.

Male workers (n=20) who had been employed for 2–14 years at a vinyl chloride polymerization plant exposed to concentrations of vinyl chloride of 1 ppm (with occasional peaks of 300 ppm) underwent

cytogenetic testing (Fucic et al. 1995). The test results were compared to those from 20 unexposed control men. Exposed individuals had higher percentages of chromosome aberrations, primarily chromatid breaks. Sister chromatid exchange frequencies were also increased in exposed workers (4–22 per cell) compared to controls (4–7 per cell). Significant changes in mitotic activity were noted among exposed workers; values for second mitosis were lower than controls and values for third mitosis were higher than controls (Fucic et al. 1995, 1997).

Genetic polymorphisms of metabolic and DNA repair genes have been associated with the sister chromatid exchange frequency in exposed workers (Wong et al. 2003b). Metabolic genotypes for CYP2E1, aldehyde dehydrogenase 2 (ALDH2) and the DNA repair genotype for x-ray repair cross complementing group1 (XRCC1) were associated with an increased risk of DNA damage in humans.

Animal studies of rats and mice exposed via inhalation to vinyl chloride have concentrated on identifying the direct effects of vinyl chloride and its metabolites on DNA. Vinyl chloride is metabolized by mixed function oxidases (MFO) to form an epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranges to form 2-chloroacetaldehyde. Reactive metabolites of vinyl chloride can be transported intercellularly from parenchymal cells to the nonparenchymal cells (Kuchenmeister et al. 1996). Many studies have characterized the mutation profile associated with DNA adducts formed by the reactive metabolites of vinyl chloride (Akasaka et al. 1997; Chiang et al. 1997; Dosanjh et al. 1994; Guichard et al. 1996; Matsuda et al. 1995; Pandya and Moriya 1996; Zhang et al. 1995; Zielinski and Hergenhahn 2000;). Four primary mutagenic DNA adducts are formed by the reactive metabolites of vinyl chloride. These are cyclic etheno-adducts that include 1,N^6-ethenoadenine, 3,N^4-ethenocytosine, N^2,3-etheno-guanine, and 1,N^2-ethenoguanine. These adducts can induce base-pair (i.e., purine-to-purine or pyrimidine-to-pyrimidine exchange) transitions during transcription (Cullinan et al. 1997; Pandya and Moriya 1996; Singer et al. 1987, 1996). 1,N^6-Ethenoadenine adducts have been demonstrated to trap topoisomerase I, affecting DNA replication and transcription (Pourquier et al. 1998). DNA crosslinks can also be formed because chloracetaldehyde is bifunctional (Singer 1994). The adduct 7-(2'-oxo-ethyl)guanine is also extensively formed in mammalian liver; however, it is quickly recognized and removed by DNA repair mechanisms. Etheno-adducts are less abundant, but more persistent because they are poorly repaired (Brandt-Rauf et al. 2000b; Whysner et al. 1996).

The identification of the etheno-nucleosides has been reported following inhalation exposure to vinyl chloride in rats (Bolt et al. 1986; Ciroussel et al. 1990; Eberle et al. 1989; Fedtke et al. 1990; Morinello et al. 2002a, 2002b; Swenberg et al. 1992). Immature rats exposed *in vivo* formed 6 times more of this

nucleoside adduct, which correlated with the age-related sensitivity to carcinogenesis in these animals (Ciroussel et al. 1990). This age-related sensitivity to DNA adduct formation was also noted in an inhalation study of lactating rats and their 10-day-old pups exposed 4 hours/day, for 5 days to 600 ppm of vinyl chloride (Fedtke et al. 1990). Concentrations of two adducts found in the liver of the pups were 4-fold higher than those found in the liver of the dams. Increased alkylation of liver DNA and increased cell proliferation were reported by Laib et al. (1989) following exposure to 600 ppm vinyl chloride for 6 hours. Young rats were apparently more susceptible to the effects of vinyl chloride, but only three male adults and two female adults were used for comparison. The concentration of ethenoguanine adducts was 2–3-fold greater in weanling rats as compared to adult rats exposed at the same dose for the time period (0, 10, 100, or 1,100 ppm, 6 hours/day for 5 days) (Morinello et al. 2002a). Rats exposed to 2,000 ppm vinyl chloride for 8 hours/day, 5 days/week, for 3 weeks beginning at 7 days of age demonstrated hepatocellular ATPase-deficient foci and alkylation of liver DNA (Gwinner et al. 1983). A study in rats exposed to 1,100 ppm vinyl chloride for 6 hours/day, 5 days/week for 1 or 4 weeks demonstrated that ethenoguanine adducts are not formed in the adult rat brain (Morinello et al. 2002b). This differential induction of DNA adducts (brain vs. liver) may relate to the direct effect of reactive intermediates at the site of metabolite generation.

The role of etheno-adducts in the carcinogenesis of vinyl chloride has been recently reviewed (Albertini et al. 2003; Barbin 1998, 1999, 2000; Kielhorn et al. 2000; Nivard and Vogel 1999; Whysner et al. 1996). Both 2-chloroethylene oxide and 2-chloroacetaldehyde can react with DNA nucleotide bases; however, 2-chloroethylene oxide is a more potent mutagen and may be the ultimate carcinogenic metabolite of vinyl chloride (Chiang et al. 1997). Etheno-adducts generate mainly base pair substitution mutations. Mutations in specific genes (i.e., *ras* oncogenes, p53 tumor suppressor gene) have been identified in vinyl chloride-induced liver tumors in rats and humans and are discussed in further detail below. Exocylic DNA adducts are excised from the DNA by glycosylase enzymes that contribute to genetic stability (Laval and Saparbaev 2001). The four primary cyclic adducts formed in DNA by the vinyl chloride metabolite chloroacetaldehyde are released by human glycosylase enzymes (Dosanjh et al. 1994; Singer and Hang 1999). The expression of the DNA repair enzyme N-methylpurine-DNA-glycosylase was shown to be deficient in nonparenchymal cells of the rat liver, which are the target cells for vinyl chloride-induced angiosarcoma (Holt et al. 2000; Swenberg et al. 1999). However, there was no difference observed in the formation of ethenoguanine adducts in hepatocytes and nonparenchymal cells immediately following vinyl chloride exposure (Morinello et al. 2002a). Together, these data suggest that cellular differences in DNA repair capacity may play a role in vinyl chloride-induced carcinogenesis. It is important to note that endogenously formed etheno-adducts are also present in humans and laboratory

animals due to a reaction between DNA and lipid peroxidation by-products. This background incidence of etheno-adducts should be taken into account when evaluating exposure to chemicals like vinyl chloride (Albertini et al. 2003; Bartsch and Nair 2000; Gonzalez-Reche et al. 2002; Swenberg et al. 2000; Watson et al. 1999; Yang et al. 2000; Zielinski and Hergenhahn 2001).

It has been suggested that members of the *ras* gene family, including Ha-*ras*, Ki-*ras*, and N-*ras*, are responsible for the control of cell proliferation and differentiation (Froment et al. 1994). DNA adducts formed by vinyl chloride metabolites can produce point mutations in these genes. Mutations of the Ki-*ras*-2 gene has been found in hepatic angiosarcomas of workers exposed to high levels of vinyl chloride; this specific gene was shown to be activated by a GC-AT transition at codons 12 and 13 (Brandt-Rauf et al. 1995; Marion et al. 1991; Weihrauch et al. 2002). Similar mutations of Ki-*ras*-2 have been found in hepatocellular carcinomas of workers exposed to vinyl chloride (Weihrauch et al. 2001a, 2001b). Hypermethylation of the p16 gene was also associated with Ki-*ras*-2 mutation in hepatocellular carcinomas from exposed workers (Weinhrauch 2001b).

Mutation of the Ki-*ras*-2 gene results in the expression of a mutant p21 protein. This mutant oncoprotein was detected in serum samples taken from vinyl chloride workers with angiosarcoma of the liver (DeVivo et al. 1994; Marion 1998). Mutant p21 protein was also detected in the serum or plasma of exposed workers without liver tumors and a relationship between the frequency of the mutant protein in serum and the intensity of vinyl chloride exposure was demonstrated in several studies (Brandt-Rauf et al. 1995; DeVivo et al. 1994; Li et al. 1998; Luo et al. 1998, 2003; Marion 1998).

Rat liver tumors induced by exposure to 500 ppm vinyl chloride were examined for mutations of the Ha-*ras*, Ki-*ras*, and N-*ras* genes (Boivin-Angele et al. 2000; Froment et al. 1994; Marion and Boivin-Angele 1999). In contrast with the studies in humans, Ki-*ras* gene mutation does not occur in rats or mice with angiosarcoma of the liver induced by vinyl chloride exposure. Rats with hepatocellular carcinoma demonstrated a AT–TA transversion of base 2 of codon 61 of the Ha-*ras* gene. This mutation was not detected in rodent angiosarcoma of the liver suggesting that there might be cell-specific factors that affect the *ras* gene. Other mutations in codons 13 and 36 of the N-*ras* A gene were found in two out of five of the liver angiosarcomas examined (Froment et al. 1994). These studies suggest differing molecular mechanisms of carcinogenesis in humans and rodents.

The p53 tumor suppressor gene is mutated in a variety of human cancers (Staib et al. 2003; Trivers et al. 1995). A study was performed to examine the p53 tumor suppressor genes and the murine double min-

2 (MDM2) proto-oncogenes from tumors of five vinyl chloride workers; four with angiosarcoma of the liver and one with hepatocellular carcinoma (Hollstein et al. 1994). The p53 tumor suppressor gene was being tested for mutation, while the MDM2 proto-oncogene was being tested for amplification. No amplification of the MDM2 gene was detected; however, adenosine-to-thymidine missense mutations were found in exons 5–8 (codons 249 and 255) of the p53 gene in two of the angiosarcoma cases. In another study, tumors (angiosarcoma of the liver) from three of six vinyl chloride workers also had adenosine-to-thymidine missense mutations in the p53 gene (codons 249, 255, and 179) (Trivers et al. 1995). Data from a study of angiosarcoma of the liver resulting from endogenous or unknown sources (i.e., no vinyl chloride exposure) indicated that p53 mutations were uncommon, providing support for the specificity of p53 mutations with vinyl chloride exposure in cases of angiosarcoma of the liver (Soini et al. 1995). The p53 gene mutation pattern in rat liver tumors (angiosarcoma and hepatocellular carcinoma) was shown to be similar to that observed in human tumors from vinyl chloride-exposed workers (Barbin et al. 1997; Marion and Boivin-Angele 1999). Mutations of the p53 gene were found in hepatocellular carcinomas from workers exposed to vinyl chloride; however, no correlation with vinyl chloride exposure occurred and the mutation pattern was thought to reflect endogenous mechanisms rather that chemical mutagenesis (Weihrauch et al. 2000). A p53 mutation at codon 179 was detected in myofibroblast-type cells isolated from a liver tumor in an exposed worker (Boivin et al. 1997). Ki-*ras* mutations were not observed in these cells. Vinyl chloride mutations of the p53 gene produce conformational effects in the expressed p53 protein that affect its function (Chen et al. 1999).

Mutant p53 protein and/or anti-p53 antibodies have been detected in the serum and plasma of vinyl chloride-exposed workers (Luo et al. 1999; Marion 1998; Smith et al. 1998; Trivers et al. 1995). A relationship between the frequency of the mutant protein or p53 antibodies in serum/plasma and the intensity of vinyl chloride exposure was demonstrated in these studies. Polymorphisms of the genes for vinyl chloride metabolism (CYP2E1) and DNA repair (x-ray cross-complementing group 1) are associated with a greater risk of p53 gene mutation and over-expression of p53 mutant protein (Li et al. 2003; Wong et al. 2002b).

Rat studies suggest that gap junctional intercellular communication mediated by connexin 37 is disturbed in angiosarcoma of the liver; however, mutation of the connexin 37 gene is considered rare (Saito et al. 1997). The incidence of hypoxanthine-guanine-phosphoribosyl-transferase (HPRT) mutants was not consistently elevated in workers exposed to vinyl chloride (Huttner and Holzapfel 1996; Liber et al. 1999). HPRT mutants were also not increased in humans accidentally exposed to vinyl chloride (Becker et al. 2001).

Vinyl chloride has not been shown to be positive for dominant lethal effects in rats exposed to up to 30,000 ppm, for 6 hours/day for 5 days (Anderson et al. 1976; Purchase et al. 1975; Short et al. 1977). The studies showed no evidence of pre- or postimplantation loss among the untreated females mated to the exposed males. These results indicate that no germinal mutations were produced by these acute exposures. Vinyl chloride induces somatic and sex-linked recessive lethal mutations in *Drosophila*, but does not induce dominant lethal mutations (Ballering et al. 1996; Giri 1995).

Vinyl chloride is mutagenic in *S. typhimurium* (Andrews et al. 1976; Bartsch et al. 1975, 1976; de Meester et al. 1980; Elmore et al. 1976; Poncelet et al. 1980; Simmon et al. 1977), but only in strains reverted by base-pair substitution by alkylating agents rather than by frameshift mutations (Bartsch et al. 1976; duPont 1992a, 1992b). Metabolic activation is necessary for any mutagenic activity in this system (Rannug et al. 1974) or for a maximal response (Simmon et al. 1977). In addition, vinyl chloride is mutagenic in the gaseous phase, but not when it is dissolved in water (Poncelet et al. 1980). The negative findings for vinyl chloride dissolved in water are most likely due to methodological problems associated with rapid evaporation and therefore do not reflect a lack of mutagenic potential.

Concentrations of vinyl chloride tested *in vitro* range from 0.275% (Shahin 1976) to 40% (duPont 1992a). Shahin (1976) reported negative results for 0.275 and 0.55% vinyl chloride in *Saccharomyces cerevisiae*. In *S. typhimurium*, a doubling of revertants has been reported to occur at about 5% vinyl chloride (Victorin and Stahlberg 1988a). Vinyl chloride was found to be mutagenic in Chinese hamster ovary cells (duPont 1992c). Workers exposed to vinyl chloride have been shown to have increased chromosomal aberrations, micronucleic counts, and sister chromatid exchange frequencies (Anderson et al. 1980; Fucic et al. 1992, 1995, 1997; Garaj-Vrhovac et al. 1990; Kucerova et al. 1979; Sinues et al. 1991; Zhao et al. 1996).

There is evidence that in *S. typhimurium* and *E. coli*, it is the oxidation of vinyl chloride to the reactive intermediates 2-chloroethylene oxide and 2-chloroacetaldehyde that is responsible for the mutagenicity of vinyl chloride (Jacobsen et al. 1989; McCann et al. 1975; Rannug et al. 1976). The S-9 fraction from surgically obtained human liver specimens was shown to metabolize vinyl chloride to electrophiles that were mutagenic to *S. typhimurium* TA1530 (Sabadie et al. 1980). Mutagenicity assays were performed by exposing the plates containing *S. typhimurium* and 150 µL human S-9 fraction to a gaseous mixture of 20% vinyl chloride in air for 4 hours. Vinyl chloride was removed after the exposure. The vinyl chloride concentration in the aqueous phase of the plates was $4x10^{-3}$ M. Incubation was continued for an

additional 48 hours. When compared with the number of revertants per plate resulting from identically prepared S-9 fractions from female strain BD IV rats, human S-9 fractions induced mutations (and presumably metabolism to a reactive electrophile) to an average 84% of the extent mediated by rat S-9. However, a 9-fold individual variation was observed.

Chloroacetaldehyde appears to be less genotoxic in yeast and Chinese hamster V79 cells than 2-chloroethylene oxide (Huberman et al. 1975; Loprieno et al. 1977) and has been shown to inhibit DNA synthesis in avian cells (Kandala et al. 1990). However, 2-chloroacetaldehyde has been shown to react directly with single-stranded DNA, which then produced base changes and subsequent reversion in *E. coli* when the DNA was inserted via phage (Jacobsen et al. 1989). Recent data have also shown 2-chloroacetaldehyde to be mutagenic in human fibroblast cells using shuttle vectors (Matsuda et al. 1995).

3.4 TOXICOKINETICS

Vinyl chloride is volatile and exposure occurs largely by inhalation. Studies in humans and animals have shown that vinyl chloride is readily absorbed through the lungs (Krajewski et al. 1980; Withey, 1976). Animal studies demonstrate that vinyl chloride is rapidly and almost completely absorbed from the gastrointestinal tract after oral exposure (Watanabe et al. 1976a; Withey 1976). A single study in monkeys, suggests that dermal absorption of vinyl chloride gas is not likely to be significant (Hefner et al. 1975a). No studies were located that reported the absorption of vinyl chloride in humans after oral or dermal exposure.

Animal studies indicate that the distribution of vinyl chloride is rapid and widespread; however, storage in the body is limited because of rapid metabolism and excretion. Metabolites of vinyl chloride have been found in the liver, kidney, spleen, skin, and brain, but tissue concentrations do not increase following repeated exposure (Bolt et al. 1976a; Butcher et al. 1977; Watanabe 1978a, 1976b). Vinyl chloride has been shown to cross the placenta after inhalation exposure (Ungvary et al. 1978). No studies were located that reported tissue distribution after inhalation, oral, or dermal exposure to vinyl chloride in humans or after dermal exposure in animals. Vinyl chloride distribution may be affected by differences in gender, age, and nutritional status.

Vinyl chloride metabolism in humans is attributed to the cytochrome P-450 monooxygenases in the liver (Ivanetich et al. 1977; Sabadie et al. 1980; Salmon 1976). The proposed metabolic pathways for vinyl

chloride are shown in Figure 3-3. Data obtained in rats indicate that metabolic pathways are consistent for both inhalation and oral exposure (Green and Hathway 1975, 1977; Watanabe and Gehring 1976; Watanabe et al. 1976a). Metabolism occurs via the oxidation of vinyl chloride by mixed function oxidases (MFO) to form an epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranges to form 2-chloroacetaldehyde. Intermediates are detoxified primarily via glutathione conjugation and conjugates are excreted in urine as substituted cysteine derivatives. Metabolism has been shown to follow first-order kinetics in rats, with enzyme saturation near 100 ppm in air or between 1 and 100 mg/kg/day for a single gavage dose (Hefner et al. 1975b; Watanabe et al. 1976a). Macromolecular binding has been attributed to the reactive intermediate 2-chloroethylene oxide, which binds to DNA and RNA (ribonucleic acid), and its reaction product, 2-chloroacetaldehyde, which binds to protein molecules (Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b). No studies were located regarding vinyl chloride metabolism in humans after oral or dermal exposure or in animals after dermal exposure. It should be noted that the toxicokinetics of vinyl chloride could be affected by compromised liver function or exposure to alcohol and other drugs and chemicals.

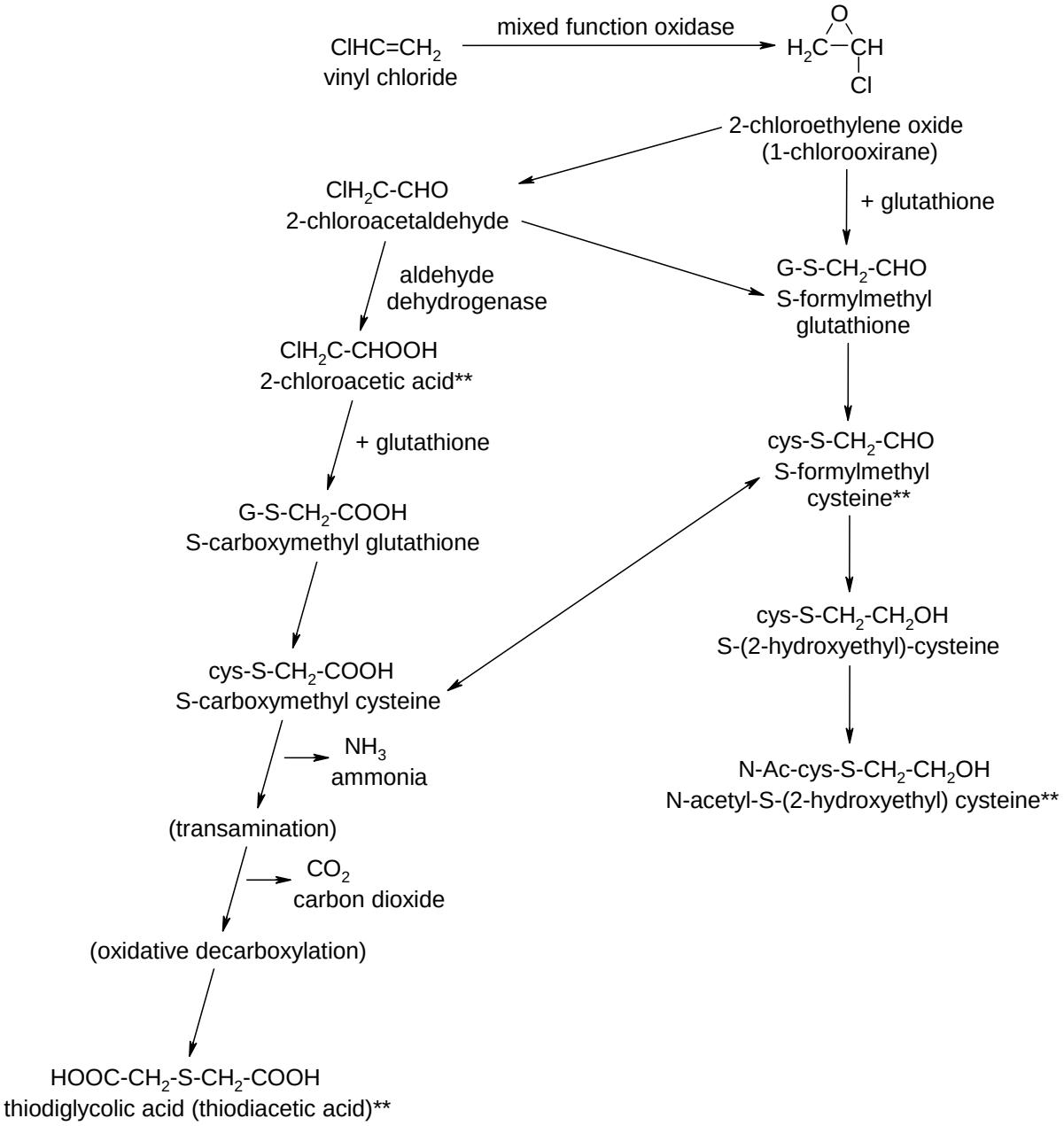
Animal studies have demonstrated that the primary route of excretion is dose-dependent (Watanabe and Gehring 1976; Watanabe et al. 1978a, 1976b). Vinyl chloride metabolites are excreted primarily in the urine following oral or inhalation exposure to low doses. At higher doses where metabolic saturation has been exceeded, vinyl chloride is exhaled as the parent compound. This was also demonstrated in humans exposed by inhalation, where exhalation of vinyl chloride was a minor pathway of elimination at low concentrations (Krajewski et al. 1980). No studies were located regarding excretion in humans after oral or dermal exposure to vinyl chloride. After dermal exposure in monkeys, most of the little vinyl chloride absorbed was excreted in exhaled air (Hefner et al. 1975a).

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Inhalation absorption of vinyl chloride is rapid in humans. Young adult male volunteers were exposed to vinyl chloride concentrations of 2.9, 5.1, 11.7, or 23.5 ppm by gas mask for 6 hours (Krajewski et al. 1980). Retention was estimated by measuring the difference between inhaled and exhaled concentrations. An average retention of 42% was estimated. Although the results varied among the individuals tested, the percentage retained was independent of the concentration inhaled. Since retention

Figure 3-3. Proposed Metabolic Pathways for Vinyl Chloride*



*Derived from Bolt et al. (1980); Cogliano and Parker (1992); Hefner et al. (1975b); Park et al. (1993); and Plugge and Safe (1977).

**Excreted in urine.

did not change with increasing vinyl chloride concentrations, it appears that saturation of the major pathway of overall metabolism did not occur in this exposure regimen.

Animal data demonstrate that the inhalation absorption of vinyl chloride occurs readily and rapidly. PBPK models that have been developed to provide quantitative estimates of uptake are discussed in Section 3.4.5. Peak blood levels occurred at 30 minutes in rats exposed (head only) to 7,000 ppm (Withey 1976). On removal from the vinyl chloride atmosphere, blood levels fell rapidly. After 2 hours, concentrations were barely detectable.

3.4.1.2 Oral Exposure

No studies were located regarding absorption in humans after oral exposure to vinyl chloride.

Several studies in rats indicate that vinyl chloride is rapidly and virtually completely absorbed from the gastrointestinal tract. Peak blood levels of vinyl chloride were observed within 10–20 minutes after dosing in rats administered single oral doses (44–92 mg/kg) of vinyl chloride in aqueous solution (Withey 1976). Peak blood levels varied from 6 to >40 µg/mL. Data from another study in which rats were administered single gavage doses of 0.05, 1, and 100 mg/kg vinyl chloride labelled with radioactive carbon (^{14}C-vinyl chloride) (in corn oil) suggested that almost complete absorption of vinyl chloride occurred (Watanabe et al. 1976a). The fraction of the administered dose recovered in the feces, roughly indicative of the proportion unabsorbed, ranged from 0.47 to 2.39%; total recovery ranged from 82.3% to 91.3%. Loss of radioactivity might be attributed either to experimental error or to incomplete sampling of the carcass. Fecal excretion was measured in rats fed 0, 1.8, 5.6, and 17.0 mg/kg/day of vinyl chloride monomer (from powdered PVC containing a high level of the monomer) (Feron et al. 1981). Fecal excretion accounted for 8, 10, and 17% of the vinyl chloride present in the low-, middle-, and high-dose groups, respectively. The investigators hypothesized that the vinyl chloride recovered from the feces was encapsulated by PVC and was not available to the rats for absorption, and that absorption of available vinyl chloride was virtually complete.

3.4.1.3 Dermal Exposure

No studies were located regarding absorption in humans after dermal exposure to vinyl chloride.

Animal data suggest that dermal absorption of vinyl chloride gas is not likely to be significant. Dermal absorption was measured in two rhesus monkeys that received full body (except head) exposure to vinyl chloride gas. It was estimated that 0.031% and 0.023% of the total available vinyl chloride was absorbed at 800 and 7,000 ppm, respectively, after a 2–2.5-hour exposure (Hefner et al. 1975a). The investigators concluded that, after short-term exposure to high concentrations, dermal absorption was far less significant than inhalation absorption. No information is available regarding dermal absorption of vinyl chloride from liquid or solid mediums.

3.4.2 Distribution

Representative vinyl chloride partition coefficients for humans, rats, mice, and hamsters can be found in Table 3-5. These partition coefficients were obtained for use in PBPK models. They were estimated using a vial equilibration technique (Air Force 1990b). Further details about how the values were obtained, including the number of experiments completed and whether the errors shown are standard deviations or standard errors, were not provided. In general, concentrations of vinyl chloride found in fat are higher than would be found in other tissues. Partition coefficients for vinyl chloride range from 10 to 20 (fat/air) and from 1 to 3 (muscle/air, blood/air, and liver/air). In animal studies, females have shown greater partitioning to fat than males.

Tissue/blood partition coefficients in male Sprague-Dawley rats, measured using a vial equilibration method, have been reported as 10±3 for fat/blood, 0.4±0.2 for muscle/blood, 0.7±0.3 for liver/blood, and 0.7±0.4 for kidney/blood (Barton et al. 1995).

3.4.2.1 Inhalation Exposure

No studies were located regarding tissue distribution in humans after inhalation of vinyl chloride.

Data from rat studies suggest that the distribution of inhaled vinyl chloride is rapid and widespread, but storage of vinyl chloride in the body is limited by rapid metabolism and excretion. In rats exposed to ^{14}C-vinyl chloride and pretreated with 6-nitro-1,2,3-benzothiadiazole to block metabolism of vinyl chloride by microsomal cytochrome P-450 oxidation pathways, the highest levels of radiolabel were located in the fat, with lesser amounts in the blood, liver, kidney, muscle, and spleen. When metabolism

Table 3-5. Vinyl Chloride Partition Coefficients

			Partition coefficient			
Species	Strain	Sex	Blood/air	Liver/air	Muscle/air	Fat/air
Rat	CDBR[a]	M	1.8±0.22	3.0±0.41	2.2±0.70	14.6±0.92
		F	2.1±0.44	1.7±0.43	1.3±0.25	19.2±0.96
	F-344[a]	M	1.6±0.33	2.0±2.0	2.1±0.40	11.8±0.81
		F	1.6±0.11	2.1±0.17	2.4±0.46	21.1±1.3
	Wistar[a]	M	2.1±0.31	2.7±0.56	2.7±0.58	10.2±1.6
		F	1.6±0.07	1.5±0.28	1.6±0.22	22.3±0.54
	Sprague-Dawley[b]	M	2.4±0.5	–	–	–
Mouse	$B6C3F_1$[a]	M	2.8±0.22	–	–	–
		F	2.6±0.14	–	–	–
	CD-1[a]	M	2.3±0.07	–	–	–
		F	2.4±0.16	–	–	–
Hamster	Golden Syrian[a]	M	2.7±0.15	3.4±0.36	2.6±0.46	14.3±5.3
		F	2.2±0.47	1.3±0.28	2.0±0.28	21.1±2.0
Human[c]	NA	NR	1.16	–	–	–

[a]Air Force 1990b; values determined using vial equilibration method.
[b]Barton et al. 1995
[c]EPA 1987g

– = no data; F = female; M = male; NA = not applicable; NR = not reported

was not blocked, the highest levels of radiolabelled metabolites were located in the liver and kidney (Buchter et al. 1977). Immediately after a 5-hour exposure to ^{14}C-vinyl chloride at 50 ppm, tissue levels of ^{14}C-activity, expressed as the percentage incorporated per gram of tissue, were highest in the kidney (2.13%) and liver (1.86%), with lower levels in the spleen (0.73%) and brain (0.17%) (Bolt et al. 1976a). Radioactivity in tissue was measured in rats 72 hours after exposure to 10 or 1,000 ppm ^{14}C-vinyl chloride for 6 hours. In order of decreasing concentration for rats exposed to 10 ppm, ^{14}C-labeled compounds (expressed as percentage), present as nonvolatile metabolites, were measured in the liver (0.14), kidney (0.08), skin (0.07), lung (0.07), muscle (0.05), carcass (0.05), plasma (0.05), and fat (0.03). For rats exposed to 1,000 ppm, radiolabel (expressed as percentage) was measured in the liver (0.15), skin (0.12), kidney (0.06), carcass (0.05), lung (0.05), muscle (0.04), fat (not detected), and plasma (not detected) (Watanabe et al. 1976b). There was no difference in the routes or rate of excretion between repeated-dose versus single-dose exposure of rats to 5,000 ppm of ^{14}C-vinyl chloride (Watanabe et al. 1978a). The concentration of radiolabel detected in tissues 72 hours after exposure revealed no statistically significant difference between rats exposed once or repeatedly to vinyl chloride. Percentages of radioactivity after 72 hours measured in tissues are as follows (for single and repeated doses, respectively): liver (0.12 and 0.16), kidney (0.06 and 0.07), skin (0.05 and 0.08), carcass (0.03 and 0.04), and fat (not detected and not detected).

Placental transfer of vinyl chloride can occur rapidly in rats. Female rats exposed to approximately 0, 2,000, 7,000, or 13,000 ppm vinyl chloride for 2.5 hours on Gd 18 showed high concentrations of vinyl chloride in maternal and fetal blood and amniotic fluid (Ungvary et al. 1978). Vinyl chloride concentrations in maternal blood were 19.02, 32.40, and 48.43 µg/mL, respectively, while fetal blood concentrations were 12.80, 22.67, and 30.52 µg/mL, respectively. Vinyl chloride concentrations in amniotic fluid were 0, 4.27, 4.93, and 13.50 µg/mL, at 2,000, 7,000, and 13,000 ppm vinyl chloride, respectively (Ungvary et al. 1978).

3.4.2.2 Oral Exposure

No studies were located regarding tissue distribution in humans after oral exposure to vinyl chloride.

The level of ^{14}C-nonvolatile metabolites was measured in tissues of rats 72 hours after single gavage doses (0.05–100 mg/kg) of ^{14}C-vinyl chloride in corn oil (Watanabe et al. 1976a). The highest levels of

radioactivity for each dose level occurred in the liver. These levels were 2–5 times higher than in the other tissues examined (skin, plasma, muscle, lung, fat, and carcass).

3.4.2.3 Dermal Exposure

No studies were located regarding tissue distribution for humans or animals after dermal exposure to vinyl chloride.

3.4.3 Metabolism

3.4.3.1 Inhalation Exposure

Metabolism can be quantitatively estimated from gas uptake experiments in which, after initial absorption of vinyl chloride, continued absorption is largely attributed to metabolism. Krajewski et al. (1980) exposed young men to vinyl chloride at concentrations of 2.9, 5.1, 11.7, and 23.5 ppm by gas mask for 6 hours. Retention was estimated by determining the difference between the inhaled and exhaled concentrations. Individual variation was present; however, the percentage retained was found to be independent of the concentration inhaled. Since the retention did not change with increasing vinyl chloride concentrations, it appears that saturation of the major metabolic pathway did not occur in this exposure regimen.

The major metabolic pathway of vinyl chloride involves oxidation by mixed-function oxidases to form a highly reactive epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranges to form 2-chloroacetaldehyde (Guengerich et al. 1979, 1981; Gwinner et al. 1983; Laib 1982). These intermediates are detoxified mainly through conjugation with glutathione catalyzed by glutathione *S*-transferase. The conjugated products are excreted in urine as substituted cysteine derivatives and include thiodiglycolic acid, *S*-formyl-methylcysteine, and *N*-acetyl-*S*-(2-hydroxyethyl)cysteine (Bolt et al. 1980; Hefner et al. 1975b). Urinary metabolites identified in rats exposed by inhalation include polar compounds at low exposure concentrations (Hefner et al. 1975b; Watanabe et al. 1976b) and 2-chloroacetic acid at high exposure concentrations (Hefner et al. 1975b).

Early work on the metabolism of vinyl chloride in animals indicated that metabolism is a dose-dependent, saturable process. Rats were exposed to vinyl chloride in a closed chamber at concentrations of about 50–

1,000 ppm for 52.5–356.3 minutes (Hefner et al. 1975b). Additional rats pretreated with ethanol (to inhibit alcohol dehydrogenase activity) or SKF 525-A (to inhibit microsomal oxidase activity) were similarly exposed. Metabolism, estimated by measuring the rate of disappearance of vinyl chloride from the closed system, followed first-order kinetics with a half-life of 86 minutes at <100 ppm. At >220 ppm, metabolism was slowed to a half-life of 261 minutes, suggesting saturation of the pathway predominant at 100 ppm. Pretreatment with ethanol depressed the rate of metabolism by approximately 83% at <100 ppm but by approximately 47% at >1,000 ppm. Pretreatment with SKF 525-A, however, had no effect at <100 ppm but depressed metabolism by 19% at >1,000 ppm. The study authors postulated alternative pathways for vinyl chloride metabolism. They suggested that at low concentrations sequential oxidation to 2-chloroethanol, 2-chloroacetaldehyde, and 2-chloroacetic acid involving alcohol dehydrogenase (inhibited by pretreatment with ethanol) appeared to be the predominant pathway. Little 2-chloroacetic acid was formed, however, possibly because 2-chloroacetaldehyde conjugated rapidly with ubiquitous sulfhydryl groups. The authors further speculated that when the alcohol dehydrogenase pathway became saturated, 2-chloroethanol could be oxidized by catalase in the presence of hydrogen peroxide (H_2O_2) to a peroxide, which could undergo subsequent dehydration to form 2-chloro-acetaldehyde. However, it appears that the only support for this proposed metabolism of vinyl chloride by alcohol dehydrogenase comes from studies demonstrating metabolic inhibition by alcohol. This is not recognized as a direct pathway for metabolism of vinyl chloride in modern PBPK modeling studies. It is possible that ethanol exerts its effects by inhibiting specific P-450 enzymes involved in the metabolic activation of vinyl chloride.

Isolated rat liver cells converted ^{14}C-vinyl chloride into nonvolatile metabolites (Hultmark et al. 1979). Using this *in vitro* technique, it was determined that metabolism was NADPH-dependent, located in the microsomal fraction of the liver, and probably involved an MFO. Pretreatment with 6-nitro-1,2,3-benzo-thiadiazole, an inhibitor of some microsomal cytochrome P-450 oxidation pathways, was sufficient to totally block the metabolism of vinyl chloride in rats exposed to 0.45 ppm in a closed system for 5 hours (Bolt et al. 1977). This observation suggests that metabolism of vinyl chloride proceeds primarily through an MFO pathway with likely production of an epoxide intermediate.

Inhalation exposure of high concentrations of vinyl chloride has also been associated with a reduction in the liver nonprotein sulfhydryl concentration in the rat (Barton et al. 1995). These results are consistent with conjugation of the metabolites of vinyl chloride with limited reserves of glutathione and/or cysteine (Bolt et al. 1976b; Hefner et al. 1975b; Jedrychowski et al. 1984; Watanabe et al. 1978b).

Saturation of metabolic pathways was observed in rats and monkeys that were exposed in a closed system to ^{14}C-vinyl chloride (Bolt et al. 1977; Buchter et al. 1980; Filser and Bolt 1979). In rats, metabolic saturation was determined to occur at approximately 250 ppm, and a metabolic rate (V_{max}) of 110 µmol/hour/kg was estimated (Bolt et al. 1977; Filser and Bolt 1979). Kinetic constants of 58 µmol/hour/kg for V_{max} and 1 µM for the K_m in male Sprague-Dawley rats have also been reported (Barton et al. 1995). In an experiment using rhesus monkeys, metabolic saturation occurred at 200 ppm, with a V_{max} of 50 µmol/hour/kg (Buchter et al. 1980). The V_{max} of 50 µmol/hour/kg that was estimated using rhesus monkeys was suggested as a closer approximation of metabolism in humans than the value of 110 µmol/hour/kg estimated for rats by Filser and Bolt (1979).

Kinetic constants for vinyl chloride metabolism have also been studied *in vitro* in rat liver microsomes (El Ghissassi et al. 1998). Vinyl chloride metabolism to reactive species followed Michaelis-Menton kinetics with a K_m of 7.42 µM and a V_{max} of 4,674 pmol/mg protein/minute. Inhibitor studies using chemical and immunological inhibitors demonstrate that vinyl chloride is metabolized primarily by CYP2E1.

Several investigators have observed the binding of nonvolatile metabolites of ^{14}C-vinyl chloride to liver macromolecules *in vitro* and in rats exposed by inhalation (Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b). In single-exposure experiments at different concentrations, the extent of macromolecular binding increased proportionately to the amount of vinyl chloride metabolized and disproportionately to the exposure concentration (Watanabe et al. 1978b). The extent of macromolecular binding was increased by repeated exposure to vinyl chloride (Watanabe et al. 1978a) and by pretreatment with phenobarbital (Guengerich and Watanabe 1979). Macromolecular binding has been attributed to the reactive intermediate 2-chloroethylene oxide, which has been shown to bind to DNA and RNA, and to its rearrangement product, 2-chloroacetaldehyde, which has been shown to bind to protein molecules (Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b).

3.4.3.2 Oral Exposure

No studies were located regarding metabolism in humans after oral exposure to vinyl chloride.

Urinary metabolites identified from rats ingesting ^{14}C-vinyl chloride are consistent with the metabolic pathways postulated for inhalation exposure, in particular with the formation of 2-chloroethylene oxide

and 2-chloroacetaldehyde. Metabolites identified include *N*-acetyl-*S*-(2-hydroxyethyl)cysteine, 2-chloroacetic acid, and thiodiglycolic acid (Green and Hathway 1975, 1977; Watanabe and Gehring 1976; Watanabe et al. 1976a). Metabolic saturation appears to occur with a single gavage dose of between 1 and 100 mg/kg/day (Watanabe et al. 1976a).

3.4.3.3 Dermal Exposure

No studies were located regarding metabolism in humans or animals after dermal exposure to vinyl chloride.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Human data suggest that exhalation of unmetabolized vinyl chloride is not an important pathway of elimination at low exposure concentrations. The mean concentration in expired air for humans exposed for 6 hours to air containing 2.9–23.5 ppm ranged from 0.21 to 1.11 ppm, representing from 7.23 to 4.73% of the inhaled concentrations, respectively (Krajewski et al. 1980).

Animal studies indicate that the importance of exhalation of vinyl chloride as a major route of excretion varies with the exposure concentration. The mode of excretion of vinyl chloride and its metabolites following inhalation exposure of animals to different concentrations reflects the saturation of metabolic pathways. The cumulative excretion of radioactivity over a 72-hour postexposure period was measured in rats exposed to 10–1,000 ppm (Watanabe and Gehring 1976; Watanabe et al. 1976b) or 5,000 ppm (Watanabe et al. 1978a) ^{14}C-vinyl chloride for 6 hours. Radioactivity expired as carbon dioxide or vinyl chloride, excreted in the urine and feces, and retained in the carcass was expressed as a percentage of the total radioactivity recovered. The results suggest that metabolism was nearly complete at 10 ppm because less than 2% of the recovered radioactivity occurred as unchanged parent compound. The predominant route for excretion of radioactive metabolites was through the urine, accounting for about 70% of the recovered radioactivity. Metabolism became saturated at 1,000 ppm, since unchanged vinyl chloride increased to 12.3% and urinary radioactivity decreased to 56.3%. At 5,000 ppm, more than half the recovered radioactivity appeared as unchanged vinyl chloride in expired air, and urinary excretion accounted for about 27% of the recovered activity. Generally, there was little change in the proportion of

recovered radioactivity excreted in the feces or exhaled as carbon dioxide. The percentage of the radioactivity retained in the carcass and tissues appeared to be somewhat decreased at 5,000 ppm compared with 10 and 1,000 ppm, suggesting preferential retention of metabolites rather than unchanged vinyl chloride. It should be noted that the trend of a greater percentage of vinyl chloride being exhaled at higher concentrations in animals is the opposite of what was observed in humans in Krajewski et al. (1980). In humans, a higher percentage of unmetabolized vinyl chloride was found in expired air at lower concentrations (Krajewski et al. 1980). However, it is possible that a reversal of this trend would occur in humans if concentrations were increased to those used in the animal studies or to concentrations closer to the K_m for human metabolism.

Pulmonary excretion of unaltered vinyl chloride in rats followed first-order kinetics regardless of exposure concentrations, with half-lives of 20.4, 22.4, and 30 minutes following 6-hour exposures at 10, 1,000, and 5,000 ppm, respectively. The urinary excretion of radioactivity was biphasic, with the second or slow phase accounting for less than 3% of the total urinary excretion. Estimated half-lives for the rapid (first-order) phase were 4.6, 4.1, and 4.5 hours, at 10, 1,000, and 5,000 ppm, respectively. Urinary metabolites included *N*-acetyl-*S*- (2-hydroxyethyl)cysteine, thiodiglycolic acid, and possibly *S*-(2-hydroxyethyl)cysteine (Watanabe et al. 1976b). Identification of these metabolites of vinyl chloride in the urine indicates that vinyl chloride is transformed in the body to a reactive metabolite, which is then detoxified by reaction with glutathione (GSH, gamma-glutamylcysteinylglycine). Subsequently the glutamic acid and glycine moieties of the tripeptide are cleaved, and the cysteine conjugate of the reactive metabolite of vinyl chloride is either acetylated or further oxidized and excreted. Thiodiglycolic acid is the major metabolite of vinyl chloride detected in the urine of exposed workers (Cheng et al. 2001). Urinary thiodiglycolic acid levels were correlated with vinyl chloride levels in air at concentrations >5 ppm.

3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to vinyl chloride.

Single oral doses of ^{14}C-vinyl chloride (0.05, 0.25, 1.0, 20, 100, and 450 mg/kg) were administered to rats, and the excretion of radioactivity was monitored over a 72-hour period (Green and Hathway 1975; Watanabe and Gehring 1976; Watanabe et al. 1976a). A striking increase in exhalation of unchanged vinyl chloride and compensatory decreases in urinary and fecal excretion of radioactivity and exhalation

of carbon dioxide were observed at >20 mg/kg, suggesting that metabolic saturation had occurred at that dosage. At less than 1.0 mg/kg, the predominant route of elimination was urinary excretion of polar metabolites.

Exhalation of unchanged vinyl chloride was generally complete within 3–4 hours, but excretion of metabolites continued for days (Green and Hathway 1975). Pulmonary excretion of vinyl chloride appeared to be monophasic at less than 1.0 mg/kg, with a half-life of about 55–58 minutes (Watanabe et al. 1976a). At 100 mg/kg, pulmonary excretion of vinyl chloride was biphasic, with half-lives of 14.4 and 40.8 minutes for the rapid and slower phases, respectively. Urinary excretion of radioactivity was biphasic, with the rapid phase accounting for more than 97% of total urinary radioactivity and having half-lives of 4.5–4.6 hours for dosages of 0.05–100 mg/kg.

Metabolites identified in the urine of orally treated rats were consistent with the formation of 2-chloroethylene oxide and 2-chloroacetaldehyde (Green and Hathway 1977; Watanabe et al. 1976a), as postulated for metabolism following inhalation exposure. The major metabolites were identified as thiodiglycolic acid and *N*-acetyl-*S*-(2-hydroxyethyl)cysteine (Watanabe et al. 1976a). *N*-Acetyl-*S*-(2-chloroethyl)cysteine and *S*-(2-chloroethyl)cysteine have also been identified as having smaller amounts of radiolabelled urea, glutamic acid, and 2-chloroacetic acid (Green and Hathway 1975).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans after dermal exposure to vinyl chloride.

When two rhesus monkeys received whole-body (except head) exposure to vinyl chloride gas (800 and 7,000 ppm) for 2–2.5 hours, although very little vinyl chloride was absorbed, most was excreted in expired air (Hefner et al. 1975a). The percentages of absorbed vinyl chloride that were exhaled were 0.028% and 0.014% at 700 and 8,000 ppm, respectively (Hefner et al. 1975a).

3.4.4.4 Other Routes of Exposure

The elimination of radioactivity following intraperitoneal administration of ^{14}C-vinyl chloride to rats resembles the pattern observed following inhalation or oral administration. Following an intraperitoneal

dose of 0.25 mg/kg, exhalation of unchanged vinyl chloride, exhalation of carbon dioxide, and urinary and fecal excretion of radioactivity accounted for 43.2, 11.0, 43.1, and 1.8% of the administered dose, respectively (Green and Hathway 1975). At 450 mg/kg, exhaled vinyl chloride increased to 96.2% of the administered dose, carbon dioxide decreased to 0.7%, urinary radioactivity decreased to 2.6%, and fecal radioactivity decreased to 0.1%.

Doses administered intravenously were eliminated very rapidly and almost entirely by exhalation of unchanged vinyl chloride. Green and Hathway (1975) administered a 0.25-mg/kg intravenous dose of ^{14}C-vinyl chloride to rats and recovered 80% of the dose within 2 minutes and 99% within 1 hour as unchanged compound in expired air.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of

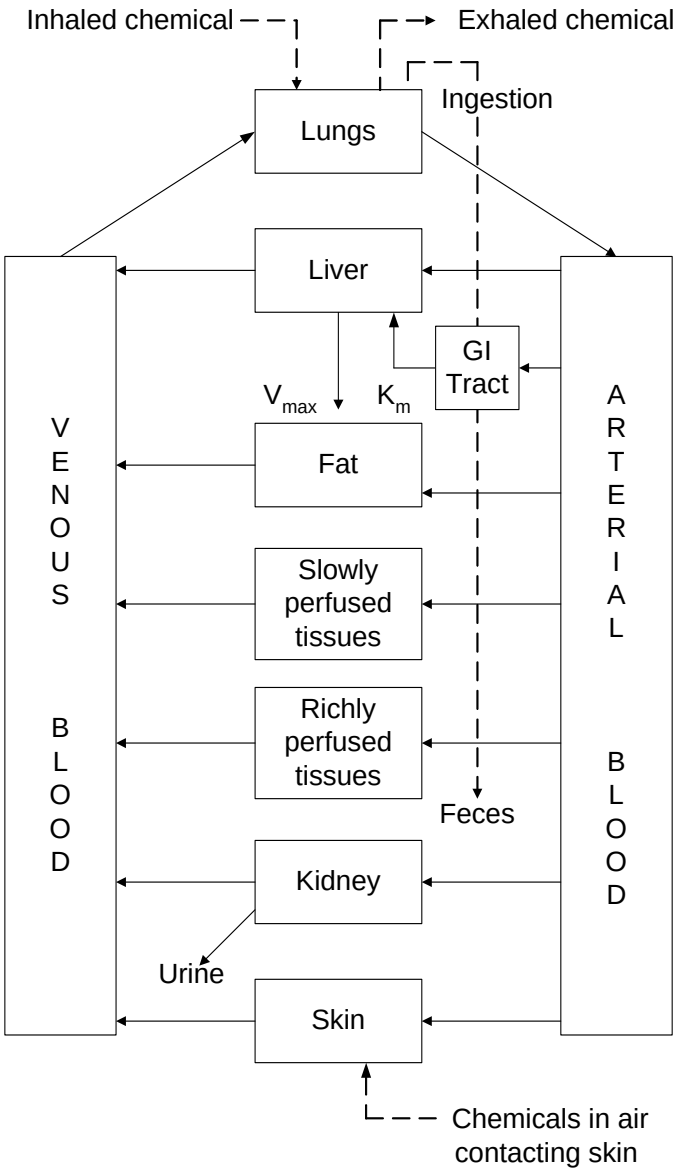
toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

PBPK models are available for vinyl chloride. The overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Summary of PBPK/PD Models

Models have been developed to predict the metabolism and distribution of vinyl chloride. EPA (1987g) developed a PBPK model to estimate the metabolized dose of vinyl chloride coupled to a multistage model to estimate cancer risk in animals. This PBPK model consists of four compartments, the liver, fat group, highly perfused tissue, and poorly perfused tissue. All metabolism was assumed to occur in the liver by one saturable pathway (Michaelis-Menten kinetics) and by a first-order metabolism pathway. The physiologic parameters used were values from an EPA draft "Reference Physiologic Parameters in Pharmacokinetic Modeling" by Dr. Curtis Travis of the Oak Ridge National Laboratory.

The dose delivery of the vinyl chloride model developed by EPA (1987g) was further validated by the Air Force (1990b) study with additional vinyl chloride metabolism studies in rats. At low concentrations, this model fit *in vivo* data in rats by Gehring et al. (1978) well, but at concentrations above 25 ppm, the model predicted a greater amount of vinyl chloride metabolism than observed. The Air Force (1990b) then made modifications in the model to improve the fit with actual data. In the first modification, both vinyl chloride and the epoxide metabolite were assumed to react with glutathione. This model had difficulty predicting glutathione depletion at high doses; for example, it predicted glutathione depletions higher than observed at 4,600–5,800 ppm vinyl chloride. The second alternative model, in which only the product of the first-order metabolism was assumed to react with glutathione, also predicted glutathione depletions higher than observed at high concentrations. To improve the model, the investigators suggested the addition of a low-affinity glutathione pathway.

Using data obtained from Wright-Patterson Air Force Base, the Air Force (1990b) extended the first glutathione conjugation model, developed in rats, to different strains of rats, mice, and hamsters. Vinyl chloride gas uptake experiments were completed in which animals were exposed to various concentrations of vinyl chloride in closed chambers for up to 6 hours, and the disappearance of vinyl chloride was monitored. The glutathione content of the animals was also measured immediately after exposure. Using data from these studies and the physiologic parameters shown in Table 3-6, the investigators estimated metabolic parameters for vinyl chloride and the rate constant for the conjugation of vinyl chloride with glutathione (Table 3-7). Using the metabolic parameters determined from the gas uptake experiments, the model predictions showed good agreement with the actual data for all the strains tested. It does not appear that the investigators further validated the model with data from studies other

Table 3-6. Physiological Parameters Used to Estimate Parameters from Vinyl Chloride Gas Uptake Experiments[a]

Parameter	Rats	Mice	Hamsters
Ventilation rate (L/hour/body weight$^{0.74}$)	14	23–25[b]	13
Total cardiac output (L/hour/body weight$^{0.74}$)	14	23–25[b]	13
Blood flow to the liver (fraction of total cardiac output)	0.25	0.24	0.24
Blood flow to highly perfused tissue (fraction of total cardiac output)	0.51	0.52	0.52
Blood flow to fat (fraction of total cardiac output)	0.09[c]	0.05	0.09
Blood flow to poorly perfused tissue (fraction of total cardiac output)	0.15[c]	0.20	0.15
Volume of tissue (L/body weight)	0.04	0.04	0.04
Volume of highly perfused tissue (L/body weight)	0.04	0.05	0.05
Volume of fat tissue (L/body weight)	0.07–0.1[d]	0.04	0.07
Volume of poorly perfused tissue (L/body weight)	0.72–0.75[d]	0.78	0.75

[a]Air Force 1990b; units of body weight were not provided.
[b]Ventilation rates and total cardiac outputs were 23 for male B6C3F$_1$ mice, 25 for female B6C3F$_1$ mice, 28 for female CD-1 mice, and 35 for male CD-1 mice.
[c]Male Wistar rats blood flow to fat = 0.08 and blood flow to slowly perfused tissue = 0.16.
[d]Female F-344 and female Wistar rats had volume of fat tissue = 0.07 and volume of slowly perfused tissue = 0.75; male F-344 and female Wistar rats had volume of fat tissue = 0.08 and volume of slowly perfused tissue = 0.74; male Wistar rats and male CDBR rats had volume of fat tissue = 0.1 and volume of slowly perfused tissue = 0.72.

Table 3-7. Estimates of Metabolic Parameters Obtained from Gas Uptake Experiments[a]

Species	Strain	Sex	V_{max}/body weight$^{0.7}$ (mg/hour/body weight$^{0.7}$)	Kfc (body weight$^{0.3}$/hour)	Kgsc (body weight$^{0.3}$/hour/µmol/L GSH)
Rat	CDBR	M	2.5	0.63	ND
		F	2.47	1.0	0.000241
	F-344	M	3.17	1.08	0.000249
		F	2.95	1.03	0.000227
	Wistar	M	3.11	0.45	0.000093
		F	2.97	1.55	0.00040
Mouse	$B6C3F_1$	M	5.89	5.5	0.000827
		F	5.53	8.93	0.00167
	CD-1	M	6.99	5.1	0.000563
		F	5.54	6.62	0.000809
Hamster	Golden Syrian	M	4.94	1.67	ND
		F	4.76	2.06	0.000330

[a]Air Force 1990b

F = female; GSH = glutathione; Kfc = first order of epoxide formation; Kgsc = rate constant for conjugation of vinyl chloride with glutathione; M = male; ND = not determined; V_{max} = maximum velocity of reaction

than those used to determine the metabolic parameters. This model was not used to estimate metabolized doses for humans because the investigators indicated that human data to estimate all the required parameters were not available. They suggested that allometry may have to be used to estimate some of the parameters for humans.

Clewell et al. (1995) used PBPK modeling coupled with a linearized multistage model to predict human cancer risk. The model again had four compartments as described for the EPA (1987g) study, and the same EPA physiologic parameters were used. Partition coefficients were from *in vitro* experiments and are shown in Table 3-4. Metabolism was modeled by two saturable pathways: one high affinity, low capacity (P450 2E1), and one low affinity, high capacity (2C11/6 and 1A1/2). The metabolic parameters used were not provided, but they were estimated from the Air Force (1990b) model. This model assumed that the metabolites (chloroethylene oxide and chloroacetaldehyde) were further degraded to carbon dioxide, or reacted with glutathione, or reacted with DNA. The parameters (not stated) for reactions of the metabolites were estimated from vinylidene chloride data (D'Souza and Andersen 1988) using appropriate allometric scaling. Based on this PBPK model and a linearized multistage model using liver angiosarcoma data from animal studies, the human risk estimates for lifetime exposure to 1 ppb vinyl chloride ranged from 1.1 to 15.7/million persons (Clewell et al. 1995). Based on the incidence of liver angiosarcoma in human epidemiological studies, the risk estimates for lifetime exposure to 1 ppb vinyl chloride were 0.4–4.22/million persons. Clewell et al. (1995) indicated that the risk estimates in the occupational exposure range using PBPK modeling are about 30–50 times lower than estimates using external dose calculations based on the linearized multistage model.

Reitz et al. (1996) also developed a PBPK model that coupled measures of delivered dose in rats to a linearized multistage model to predict the incidence of hepatic angiosarcoma in mice and humans. The model incorporated four compartments—fat, muscle, rapidly perfused tissues, and liver. Physiological parameters in the model were based on similar ones used in an earlier multispecies PBPK model developed for methylene chloride. Partition coefficients were estimated by vial equilibration techniques similar to those described in the Air Force (1990b) study. Metabolic rate constants were obtained from *in vivo* gas uptake experiments performed at Wright-Patterson Air Force Base.

Based on the PBPK-based procedure utilized by Reitz et al. (1996), the predicted human risk estimates ranged from about 200 cases/100,000 (for workers employed 10 years at a plant where the TWA was 50 ppm) to almost 4,000 cases/100,000 in workers employed for 20 years in a plant where the TWA was 2,000 ppm. The predictions of human risk were compared with the data reported by Simonato et al.

(1991). The predictions of angiosarcoma incidence in humans were almost an order of magnitude higher than actually observed in exposed human populations, and were more than two orders of magnitude lower than risk estimations that did not utilize pharmacokinetic data.

Clewell et al. (2001) futher refined the PBPK model for vinyl chloride and this model was applied by the EPA to develop quantitative toxicity values for vinyl chloride (i.e., RfD, RfC, inhalation unit risk, oral slope factor) (EPA 2000). The model had four compartments and metabolism was modeled by two saturable pathways: one high affinity, low capacity (P450 2E1), and one low affinity, high capacity (2C11/6 and 1A1/2). A description of glutathione kinetics was also included in the model. Cancer risk estimates in the occupational exposure range calculated using the PBPK model were consistent with risk estimates from epidemiological studies and were approximately 80-fold lower than cancer risk estimates from animal studies without PBPK modeling. The inhalation portion of the PBPK model is well documented with experimental inhalation data sufficient to ensure a high degree of confidence in the derived dose metrics. Less confidence is associated with the oral dose metrics due to the limited experimental data available (EPA 2000).

The Clewell et al. (2001) model was also recently applied to evaluate the potential impact of age- and gender-specific pharmacokinetic differences on the dosimetry of vinyl chloride (Clewell et al. 2004). The rate of metabolite production per volume of liver was estimated to rise rapidly from birth until about age 16, after which it remains relatively constant before rising again late in life. Other factors that may affect vinyl chloride toxicity at early life stages include the presence of fetal P450s and the level of glutathione transferase.

The PBPK model described in Clewell et al. (2001) and EPA (2000) was used to derive the chronic-duration oral MRL. The chronic oral MRL for vinyl chloride is based on the same critical effect as that used by EPA (2000) to derive the RfD for vinyl chloride (i.e., the NOAEL for liver cell polymorphism in the oral rat study of Til et al. 1983, 1991). Source code and parameter values for running the rat and human models in Advance Continuous Simulation Language (ACSL) were transcribed from Appendix C of EPA (2000). Exposures in the Til et al. (1983, 1991) rat dietary study were simulated as 4-hour oral exposures with the NOAEL dose for liver effects of 0.17 mg/kg/day. A 4-hour feeding period was used in the study due to the rapid evaporative loss of vinyl chloride from the food. The total amount of vinyl chloride metabolized in 24 hours per liter of liver volume was the rat internal dose metric that was used in determining the human dose that would result in an equivalent human dose metric. One kilogram of liver was assumed to have an approximate volume of 1 L. Dose metrics reflect the cumulative amount of vinyl

chloride metabolized over the 24-hour period. The human model was run iteratively, until the model converged with the internal dose estimate for the rat (3.16 mg/L liver). The human dose was assumed to be uniformly distributed over a 24-hour period with the resulting human equivalent dose of 0.09 mg/kg/day. Therefore, the human equivalent dose of 0.09 mg/kg/day, associated with the rat NOAEL of 0.17 mg/kg/day (Til et al. 1983, 1991), served as the basis for the chronic-duration oral MRL for vinyl chloride. A total uncertainty factor of 30 (3 for extrapolating from animals to humans using a dose metric conversion and 10 for human variability) was applied to yield the chronic-duration oral MRL of 0.003 mg/kg/day (see Appendix A for more detailed information regarding the application of the PBPK modeling in deriving the chronic-duration oral MRL for vinyl chloride).

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. Vinyl chloride appears to be rapidly and completely absorbed following inhalation and oral exposure (Bolt et al. 1977; Krajewski et al. 1980; Watanabe et al. 1976a; Withey 1976).

Distribution. Distribution of vinyl chloride in the body is rapid and widespread. Storage is limited by rapid metabolism and excretion (Bolt et al. 1976a).

Metabolism. Vinyl chloride is metabolized by mixed function oxidases (MFO) to form an epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranges to form 2-chloroacetaldehyde. Reactive metabolites of vinyl chloride are detoxified by a reaction with glutathione. The glutamic acid and glycine moieties of the tripeptide are cleaved, and the cysteine conjugate of the reactive metabolite is either acetylated or further oxidized and excreted.

Excretion. The primary route of excretion of metabolites of vinyl chloride is through urine. Urinary metabolites that have been identified include *N*-acetyl-*S*-(2-hydroxyethyl)cysteine, thiodiglycolic acid, and possibly *S*-(2-hydroxyethyl)cysteine (Watanabe et al. 1976b). Exhalation of unmetabolized vinyl chloride is not an important pathway of elimination by humans after exposure to low concentrations. The importance of exhalation of vinyl chloride varies with the exposure concentration. At low exposure concentrations, little vinyl chloride is excreted unchanged in exhaled air. However, vinyl chloride can be excreted unchanged in exhaled air if metabolic pathways become saturated at high exposure concentrations (Green and Hathway 1975; Watanabe and Gehring 1976; Watanabe et al. 1976a, 1978a).

3.5.2 Mechanisms of Toxicity

The mechanisms of toxicity for noncancer effects of vinyl chloride have not been completely elucidated. Vinyl chloride disease exhibits many of the characteristics of autoimmune diseases (Raynaud's phenomenon and scleroderma). B-cell proliferation, hyperimmunoglobulinemia, and complement activation, as well as increased circulating immune complexes or cryoglobulinemia, have been noted in affected workers, indicating stimulation of immune response (Bogdanikowa and Zawilska 1984; Grainger et al. 1980; Ward 1976). Mechanisms for the vascular changes, such as those occurring with Raynaud's phenomenon, have been proposed by Grainger et al. (1980) and Ward (1976). According to these mechanisms, a reactive vinyl chloride intermediate metabolite, such as 2-chloroethylene oxide or 2-chloroacetaldehyde, binds to a protein such as IgG. The altered protein initiates an immune response, with deposition of immune products along the vascular endothelium. Circulating immune complexes are proposed to precipitate in response to exposure to the cold, and these precipitates are proposed to produce blockage of the small vessels. Resorptive bone changes in the fingers, also characteristic of vinyl chloride disease, may be due to activation of osteoclast secondary to vascular insufficiency in the finger tips, but this mechanism has not been conclusively demonstrated. Scleroderma is an autoimmune disease of unknown etiology. It is characterized clinically by cutaneous and visceral fibrosis and can range from limited skin involvement to extensive cutaneous sclerosis with internal organ changes. It has been proposed that fetal cells may be involved in the pathogenesis of scleroderma. An increase in the number of microchimeric cells of fetal origin was reportedly associated with dermal fibrosis in mice injected with vinyl chloride (Christner et al. 2001).

It has been hypothesized that cardiac arrhythmia reported after vinyl chloride exposure may result from sensitization of the heart to circulatory catecholamines, as occurs with other halogenated hydrocarbons. This was demonstrated in a dog study where the EC_{50} for cardiac sensitization was determined to be 50,000 ppm (Clark and Tinston 1973). Cardiac sensitization by halogenated hydrocarbons generally occurs at very high air concentrations (0.5–90%) (Brock et al. 2003). Therefore, it appears unlikely that persons exposed to low levels of vinyl chloride will experience these effects.

Peripheral nervous system symptoms such as paresthesia, numbness, weakness, warmth in the extremities, and pain in the fingers have been reported after vinyl chloride exposure (Langauer-Lewowicka et al. 1983; NIOSH 1977; Suciu et al. 1963, 1975). It is not known whether these effects

represent direct adverse effects of vinyl chloride on peripheral nerves or whether they are associated with tissue anoxia due to vascular insufficiency.

Vinyl chloride is a known human and animal carcinogen. It has been associated with both an increased incidence of hepatic angiosarcomas and hepatotoxicity. The mechanism for these liver effects has been studied to some extent. Vinyl chloride is metabolized by mixed function oxidases (MFO) to form an epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranges to form 2-chloro-acetaldehyde. Reactive metabolites of vinyl chloride can be transported intercellularly from parenchymal cells to the nonparenchymal cells (Kuchenmeister et al. 1996). Many studies have characterized the mutation profile associated with DNA adducts formed by the reactive metabolites of vinyl chloride (Akasaka et al. 1997; Chiang et al. 1997; Dosanjh et al. 1994; Guichard et al. 1996; Matsuda et al. 1995; Pandya and Moriya 1996; Zhang et al. 1995; Zielinski and Hergenhahn 2000). Four primary DNA adducts are formed by the reactive metabolites of vinyl chloride. These are cyclic etheno-adducts that include 1,N^6-ethenoadenine, 3,N^4-ethenocytosine, N^2,3-ethenoguanine, and 1,N^2-ethenoguanine. These adducts can produce base-pair (i.e., purine-to-purine or pyrimidine-to-pyrimidine exchange) transitions during transcription (Cullinan et al. 1997; Pandya and Moriya 1996; Singer et al. 1987, 1996). DNA crosslinks can also be formed because chloracetaldehyde is bifunctional (Singer 1994).

The role of etheno-adducts in the carcinogenesis of vinyl chloride has been recently reviewed (Albertini et al. 2003, Barbin 1998, 2000; Kielhorn et al. 2000; Whysner et al. 1996). 2-Chloroethylene oxide and 2-chloroacetaldehyde can both react with DNA nucleotide bases; however, 2-chloroethylene oxide is a more potent mutagen and may be the ultimate carcinogenic metabolite of vinyl chloride (Chiang et al. 1997). Etheno-adducts generate mainly base pair substitiution mutations. Mutations in specific genes (i.e., *ras* oncogenes, p53 tumor suppressor gene) have been identified in vinyl chloride-induced liver tumors in rats and humans and are discussed in further detail in Section 3.3.

The mechanisms for clastogenic effects of vinyl chloride exposure were examined by Fucic et al. (1990). Since chromatid and bichromatid breaks most frequently occurred in the terminal A, B, and C group chromosomes, these investigators suggested that vinyl chloride or its metabolites might interact with specific sites along the chromosome. This implies that the carcinogenicity induced by vinyl chloride can be explained in part by its nonrandom interaction with particular genes.

Liver toxicity has been demonstrated in workers exposed vinyl chloride (Berk et al. 1975; Falk et al. 1974; Gedigke et al. 1975; Ho et al. 1991; Jones and Smith 1982; Lilis et al. 1975; Liss et al. 1985;

Marsteller et al. 1975; NIOSH 1977; Popper and Thomas 1975; Suciu et al. 1975; Tamburro et al. 1984; Vihko et al. 1984). The mechanism for liver toxicity is thought to be related to the production of reactive metabolites that covalently bind to liver proteins, resulting in cellular toxicity. The intermediary metabolites, 2-chloroethylene oxide and 2-chloroacetaldehyde, bind to macromolecules in the body. 2-Chloroethylene oxide is believed to bind primarily to DNA and RNA, whereas 2-chloroacetaldehyde binds primarily to proteins (Bolt 1986; Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b).

3.5.3 Animal-to-Human Extrapolations

Limited information is available regarding the toxicokinetic differences between species. Toxicokinetic data in humans are limited (Krajewski et al. 1980; Sabadie et al. 1980), but a primate study suggested that metabolism may saturate at lower concentrations in primates than in rats (Buchter et al. 1980), which is suggestive of a lower saturation point in humans. Exposure concentrations greater than about 300–400 ppm in the primate study showed saturation characteristics (Buchter et al. 1980). PBPK models have been developed to predict the metabolism and distribution of vinyl chloride in laboratory animals and humans (see Section 3.4.5). The most recent PBPK model for vinyl chloride (Clewell et al. 2001) was applied by the EPA to develop quantitative toxicity values for vinyl chloride (i.e., RfD, RfC, inhalation unit risk, oral slope factor) (EPA 2000). The model had four compartments and metabolism was modeled by two saturable pathways: one high affinity, low capacity (P450 2E1), and one low affinity, high capacity (2C11/6 and 1A1/2). A description of glutathione kinetics was also included in the model. Cancer risk estimates calculated using the PBPK model were consistent with risk estimates from epidemiological studies.

Correlation of toxic effects between humans and animals with regard to respiratory, cardiovascular, hematological, hepatic, dermal, immunological, neurological, reproductive, and cancer effects has been noted. Renal effects, including increased relative kidney weight and an increase in severity of tubular nephrosis, have been reported in several rat studies (Bi et al. 1985; Feron and Kroes 1979; Feron et al. 1979a), but no evidence of renal effects has been shown in humans. Thus, it is unclear whether the renal effects reported in rats represent a lesion that can be attributed to vinyl chloride exposure that is unique to rats or whether the effects represent an increase in severity of a naturally occurring lesion. From the limited data available, however, it does not appear that the rat is the most appropriate species for use in studies of renal toxicity.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects produced by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may produce toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral functions. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Vinyl chloride has not been classified as an endocrine modulator; however, adverse reproductive and developmental effects have been reported in human and laboratory animal studies. Effects on the thyroid gland have also been reported.

A number of case studies of male workers occupationally exposed to vinyl chloride report sexual impotence, loss of libido, and decreased androgen secretion (Suciu et al. 1975; Veltman et al. 1975; Walker 1976). Preeclampsia (i.e., elevated blood pressure and edema during pregnancy) was reported in female workers exposed to vinyl chloride (Bao et al. 1988). Animal studies indicate that exposure to vinyl chloride can result in a decrease in testicular function (Bi et al. 1985; Sokal et al. 1980); however, these effect appears to be due to direct toxicity at the target organ and are not related to a hormone-mediated mechanism of action.

Reproductive capability was not affected in a 2-generation inhalation reproductive toxicity study in rats (Thornton et al. 2002). No effects were seen in body weight, feed consumption, ability to reproduce, gestation index or length, or pre- and postweaning developmental landmarks. Sperm counts, motility, and morphology were also unaffected by vinyl chloride exposure. Changes were observed in liver weights and/or histopathological alterations in the liver of F_0 and F_1 generation male and female rats. No effect was observed on male fertility or pre- or postimplantation loss in mice following an acute exposure to vinyl chloride (i.e., 30,000 ppm, 6 hours/day, 5 days/week) (Anderson et al. 1976). In contrast, exposure of male rats to concentrations as low as 250 ppm for 6 hours/day, 5 days/week for 11 weeks produced a decrease in the ratio of pregnant to mated females, indicating a decrease in male fertility; this effect was not observed at 50 ppm (Short et al. 1977).

Although evidence has been presented indicating that members of communities with nearby vinyl chloride polymerization facilities have significantly greater incidences of some forms of developmental toxicity, these studies failed to demonstrate a statistically significant correlation between the developmental toxicity and either parental occupation or proximity to the facility (Edmonds et al. 1978; Infante et al. 1976b; Rosenman et al. 1989; Theriault et al. 1983). Vinyl chloride did not correlate with changes in gender ratio, birth weight or height, perinatal mortality, or the incidence of congenital abnormalities in mothers occupationally exposed to vinyl chloride for more than 1 year (Bao et al. 1988).

There are inconsistencies in the developmental toxicity database for the vinyl chloride. In general, vinyl chloride produced minor developmental effects in laboratory animals (i.e., delayed ossification) only at concentrations that were significantly toxic to maternal animals. Maternal toxicity was evident in mice, rats, and rabbits exposed throughout the period of organogenesis. Adverse fetal effects included delayed ossification (all species), increased crown-rump length (mice and rats), and vertebral lumbar spurs (rats). Mice were the most sensitive species investigated (John et al. 1977, 1981). Ungvary et al. (1978) reported a significant increase in resorptions in rats exposed to vinyl chloride during the first trimester of

pregnancy. Increased liver-to-body weight ratios were observed in maternal animals exposed during the first and second trimesters, but no histopathologic alterations were found. Continuous exposure of rats to vinyl chloride throughout gestation resulted in decreased fetal weight and increased early postimplantation loss, hematomas, and hydrocephaly with intracerebral hematoma. Weanling rats displayed hepatotoxic effects including decreased bile enzyme activity, decreased bile secretion, decreased cholic acid content, and increased hexobarbital sleep time. No histological data on the livers of pups, or information regarding maternal health were presented (Mirkova et al. 1978).

In contrast with previous studies, no adverse effects were reported in an embryo-fetal developmental toxicity study conducted in rats exposed to similar concentrations of vinyl chloride via inhalation (Thornton et al. 2002). Embryo-fetal developmental parameters including uterine implantation, fetal gender distribution, fetal body weight, and fetal malformations and variations were not affected by vinyl chloride exposure. Vinyl chloride produced a slight decrease in maternal body weight gain at all exposure levels; however, no changes were observed in feed consumption, clinical signs, or postmortem gross findings. Maternal liver and kidney weights were increased relative to total body weight.

The developmental toxicity of vinyl chloride was examined using an *in vitro* whole embryo culture system (Zhao et al. 1996). Vinyl chloride induced embryo growth retardation, but was not shown to be teratogenic in the rat *in vitro* whole embryo culture system.

A study of workers exposed to vinyl chloride in PVC manufacturing plants reported that most workers who presented with scleroderma were shown to have thyroid insufficiency (Suciu et al. 1963). No histopathological effects on the adrenals were reported in guinea pigs exposed to 400,000 ppm for 30 minutes (Mastromatteo et al. 1960). Rats exposed to 30,000 ppm vinyl chloride 5 days/week, 4 hours/day for 12 months, were found to have colloid goiter and markedly increased numbers of perifollicular cells (Viola 1970).

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential adverse health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure and the nature of their response to toxicants. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to adverse health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. Vulnerability in children will also be depend on physiological status, presence of infectious agents, and exposure to other chemicals. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

No studies were located that specifically address the effects of vinyl chloride in children. The effects that have been reported to occur in humans come almost exclusively from studies of workers exposed to high concentrations of vinyl chloride by inhalation. Although the effects observed in human adults could also be observed in children, it is important to note that occupational exposure concentrations are likely to be much greater than environmental levels to which children might be exposed. The toxicological effects reported in adult vinyl chloride workers include cardiovascular, gastric, hematologic, musculoskeletal, hepatic, endocrine, dermal, ocular, immunologic, neurologic, and reproductive effects as well as cancer and death.

Some epidemiologic studies (Infante 1976; Infante et al. 1976a, 1976b; NIOSH 1977) have suggested an association between birth defects and vinyl chloride exposure of the parents of affected children. However, the design and analysis of these studies has been criticized (Hatch et al. 1981; Stallones 1987). Some inhalation studies with animals have suggested that vinyl chloride is a developmental toxicant (i.e., produces delayed ossification) at doses that also produce maternal toxicity (John et al. 1977, 1981; Mirkova et al. 1978; Sal'nikova and Kotsovskaya 1980; Ungvary et al. 1978). However, no adverse effects on embryo-fetal development were noted in a recent inhalation study in rats conducted using similar concentrations of vinyl chloride (Thornton et al. 2002).

Carcinogenicity studies with animals indicate that some of the adverse health effects of vinyl chloride are dependent on the age of the animal at the time of the exposure. Thus, higher death rates were observed when 2-month-old female hamsters, mice, and rats (equivalent to adolescent humans) were exposed to vinyl chloride in the air for 12 months than when 8- or 14-month-old animals were exposed (Drew et al. 1983). Lifetime cancer risk was also dependent on the age of the animals at the time of exposure to vinyl chloride. The incidence of hemangiosarcoma of the liver, skin, and spleen, and angiosarcoma of the stomach was greater in animals exposed by inhalation for 12 months starting immediately after weaning than in animals that were 1 year older at the time of exposure (Drew et al. 1983). The incidence of mammary gland carcinoma was higher in 2- or 8-month-old hamsters exposed to 200 ppm vinyl chloride for 6 months than in 14- or 20-month-old hamsters exposed to the same concentration and for the same

duration (Drew et al. 1983). These results demonstrate the importance of the latency period for vinyl chloride-induced carcinogenesis. Animals that were exposed at a younger age had a longer post-exposure period for the development of tumors. It is difficult to assess the sensitivity of younger animals to cancer in this study because the same exposure concentrations were used for each age group. Exposures were most effective in producing cancer when started early in life (Drew et al. 1983).

Maltoni et al. (1981) evaluated the effect of vinyl chloride dosing on liver carcinogenicity in Sprague-Dawley rats. Rats were exposed to 0, 6,000, or 10,000 ppm vinyl chloride for 100 hours, beginning either at 1 day or at 13 weeks of age. The incidence of angiosarcoma of the liver in newborn rats exposed for only 5 weeks was higher than the incidence observed in rats exposed for 52 weeks beginning at 13 weeks. Hepatoma incidence was approximately 50% in newborn rats exposed for 5 weeks, but did not occur in rats exposed for 52 weeks after maturity. The increased tumor incidence combined with the production additional tumor types (i.e., angiosarcomas and hepatomas) suggest that newborn rats may be more sensitive to vinyl-chloride induced carcinogenicity.

An age increase in DNA adduct formation was noted in an inhalation study of lactating rats and their 10-day-old pups exposed to 600 ppm of vinyl chloride for 4 hours/day, for 5 days to (Fedtke et al. 1990). Concentrations of two adducts found in liver of pups were 4-fold higher than those found in liver of dams; however, pups were exposed to contaminated breast milk in addition to air concentrations vinyl chloride. In another study, immature rats exposed to vinyl chloride formed 6 times more etheno-nucleosides compared with adults (Ciroussel et al. 1990). The concentration of ethenoguanine adducts was 2–3-fold greater in weanling rats as compared to adult rats exposed at the same dose for the time period (0, 10, 100, or 1,100 ppm, 6 hours/day for 5 days) (Morinello et al. 2002a).

Vinyl chloride induced preneoplastic foci in newborn rats, but not in mature rats (Laib et al. 1985). A study with newborn male or female Wistar rats exposed to 2,000 ppm vinyl chloride indicated that the induction of preneoplastic hepatocellular lesions in rats by vinyl chloride is restricted to an early stage in the life of the animals. The early-life stage sensitivity to the induction of tumors in animals exposed to vinyl chloride appears to be related to the induction by vinyl chloride of hepatic adenosine-5’-triphos-phatase (ATPase) deficient enzyme altered foci, which are putative precursors of hepatocellular carcinoma.

Taken together, the studies cited above suggest an early life stage sensitivity to vinyl chloride carcinogenicity (Cogliano et al. 1996). EPA has recommended an adjustment of the cancer risk estimates to account for early life-stage sensitivity to vinyl chloride (EPA 2000; Ginsberg 2003).

No studies were located that specifically address the toxicokinetics of vinyl chloride in children; however, the toxicokinetic behavior of vinyl chloride in children is expected to be similar to that in adults. An evaluation of pharmacokinetic differences across life stages suggests that the largest difference in pharmacokinetics occurs during the perinatal period (Gentry et al. 2003). The most important factor appears to be the potential for decreased clearance due to immature metabolic enzymes systems; however, an analysis of CYP2E1 levels during development suggests that protein levels and enzyme activity in children between 1 and 10 years old are comparable to adults (EPA 2001). This enzyme is not expressed in the embryonic liver, but rapidly increases during the first 24 hours after birth. Young children appear capable of metabolizing vinyl chloride to reactive intermediates that form DNA adducts that lead to cancer. A PBPK model was also recently applied to evaluate the potential impact of age- and gender-specific pharmacokinetic differences on the dosimetry of vinyl chloride (Clewell et al. 2004). The rate of metabolite production per volume of liver was estimated to rise rapidly from birth until about age 16, after which it remains relatively constant before rising again late in life. The data on CYP2E1 levels in the developing organism suggests that early life stage sensitivity to vinyl chloride-induced cancer is not solely due to an increase in the production of reactive intermediates via this isozyme. Fetal CYP isoforms may play a role in metabolism of vinyl chloride to reactive intermediates in the fetus and neonate. Glutathione conjugation may also differ in the developing organism. DNA repair capacity and other pharmacodynamic factors may also be associated with an early life stage susceptibility to cancer.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in

readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to vinyl chloride are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects produced by vinyl chloride are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 “Populations That Are Unusually Susceptible”.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Vinyl Chloride

Exposure to vinyl chloride may be monitored to some extent by the identification and quantitation of a number of parameters. For example, following acute exposure to moderate-to-high levels, vinyl chloride can be measured in expired air. The expiration of vinyl chloride follows first-order kinetics; therefore, this parameter may be directly correlated with exposure levels (Baretta et al. 1969). This measure may provide the most direct evidence of vinyl chloride exposure. However, measurement of exposure by this technique is limited by the rapidity of excretion of vinyl chloride in expired air. The half-life of vinyl chloride in expired air has been determined to be between 20 and 30 minutes following an inhalation

exposure and to be approximately 60 minutes following oral dosing (Watanabe and Gehring 1976; Watanabe et al. 1976b, 1978a, 1978b). Thus, testing must be initiated as soon as possible following termination of exposure. Furthermore, measurement of vinyl chloride in expired air has limited utility for low-level exposures (<50 ppm) because of competition with absorption and rapid metabolic processes (Baretta et al. 1969). In addition, it provides no information on the duration of exposure.

Thiodiglycolic acid is a major metabolite of vinyl chloride that is excreted in the urine. Measurement of thiodiglycolic acid in urine has been used to monitor workers occupationally exposed to vinyl chloride (Cheng et al. 2001; Müller et al. 1979). However, although this metabolite is used to estimate levels of exposure, the amount of thiodiglycolic acid in the urine varies according to individual metabolic idiosyncracies. Also, metabolism of vinyl chloride to thiodiglycolic acid is a saturable process. Therefore, when exposure exceeds a certain level, the excretion of vinyl chloride as thiodiglycolic acid will plateau (Watanabe and Gehring 1976). Furthermore, the rate of metabolism of vinyl chloride to thiodiglycolic acid may be influenced by the presence of liver disease, ethanol, or certain other substances such as barbiturates (Hefner et al. 1975b) (also see Section 3.4). Similar to the measurement of vinyl chloride in expired air, the measurement of thiodiglycolic acid must take place shortly after exposure because of the rapidity of its excretion. The half-life for excretion of thiodiglycolic acid following an acute exposure is between 4 and 5 hours (Watanabe and Gehring 1976; Watanabe et al. 1978a, 1978b). Cheng et al. (2001) suggests that urinary thiodiglycolic acid levels should not be measured at the end of a work shift, but are best detected at the beginning of the following work day. Finally, excretion of thiodiglycolic acid is not unique to exposure to vinyl chloride. For example, thiodiglycolic acid may be excreted in the urine as the result of exposure to vinylidene chloride, ethylene oxide, or 2,2-dichloro-ethylether (Norpoth et al. 1986; Pettit 1986). Also, infants delivered prematurely have been found to have high levels of urinary thiodiglycolic acid. A correlation was observed between the thiodiglycolic acid levels and the number of weeks that the infant was born prematurely. The origin of this thiodiglycolic acid is unknown, but is not believed to be associated with vinyl chloride exposure (Pettit 1986).

The intermediary metabolites, 2-chloroethylene oxide and 2-chloroacetaldehyde, bind to macromolecules in the body. 2-Chloroethylene oxide is believed to bind primarily to DNA and RNA, whereas 2-chloroacetaldehyde binds primarily to proteins (Bolt 1986; Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b). Two of the DNA adducts that are formed are 1,N^6-etheno-adenosine and 3,N^4-ethenocytidine. Monoclonal antibodies for these DNA adducts have been isolated and used in enzyme-linked immunosorbent assays (ELISA) to quantify these ethenoderivatives in biological samples (Eberle et al. 1989; Young and Santella 1988).

Measurement of DNA adducts may be useful in estimating vinyl chloride exposure. However, this technique is of limited value for quantifying levels of exposure because formation of these products will be influenced by variability in vinyl chloride metabolism. Also, their persistence in tissues will be influenced by the rate of DNA metabolism and repair. Furthermore, the DNA adducts, for which monoclonal antibodies have been isolated, are also formed as a result of exposure to vinyl bromide, ethyl carbamate, acrylonitrile, 2-cyanoethylene, and 1,2-dichloroethane (Bolt et al. 1986; Svensson and Osterman-Golkar 1986). See Section 3.4 for additional information on the kinetics of vinyl chloride.

Ethenoguanine adducts have been quantified in human urine using high performance liquid chromatography and tandem mass spectrometry (Gonzalez-Reche et al. 2002). Etheno-adducts are removed from DNA through base excision repair and excreted in the urine where they can be measured using this technique. This method would also include the measurement of endogenously formed etheno-adducts; thus, it is critical to determine the background level of urinary adducts in a control population.

Vinyl chloride-induced genetic alterations have been identified in the Ki-*ras* oncogene and the p53 tumor suppressor gene, and oncoproteins and p53 antibodies have been detected in the serum of cancer patients with angiosarcoma (see Section 3.3). Immunological techniques have been used to detect the presence of Asp13p21 (oncoprotein for mutation of the Ki-*ras* gene), p53 mutant protein, and p53 antibodies in the serum of exposed workers (Brandt-Rauf et al. 2000a, 2000b; Marion 1998). Statistical analyses suggest a relationship between vinyl chloride exposure and the presence of these serum biomarkers; however, the predictive value of these biomarkers for development of cancer is not known.

The micronucleus assay, performed using peripheral lymphocytes of 32 vinyl chloride workers, was used to indicate the time elapsed since the last vinyl chloride exposure occurred (Fucic et al. 1994, 1997). The study showed a decrease in the frequency of micronuclei and mitotic activity in proportion to the length of the interval after the last vinyl chloride exposure. For the group with 10 years of employment, the percentage of micronuclei decreased from 12.82 when exposure occurred on the day of blood sampling to 3.16 when the last exposure occurred 90 days before blood sampling (Fucic et al. 1994). Similar changes were noted when the mean duration of employment was 5 years. However, this use of the micronucleus assay must take into account the total duration of exposure.

Exposure to vinyl chloride may also be estimated to some extent by the presence of certain symptoms known to be closely associated with vinyl chloride exposure. The exposure may have occurred even if the symptoms were not found upon examination, but their presence could be indicative of exposure. For

example, a syndrome known as vinyl chloride disease has been identified in workers occupationally exposed to vinyl chloride. This syndrome includes Raynaud's phenomenon, acroosteolysis of the distal phalanges of the fingers, and scleroderma-like changes in the hands and forearms (also see Section 3.2). Although this syndrome resembles systemic sclerosis, a differential diagnosis may be made based on the absence of antinuclear antibodies from the blood of those afflicted with vinyl chloride disease (Black et al. 1983, 1986). The occurrence of vinyl chloride disease in highly exposed worker populations is about 3%, and susceptibility appears to be genetically related (Black et al. 1983, 1986). Symptoms of vinyl chloride disease are unlikely to occur in hazardous waste site conditions because of predicted low levels of exposure. Absence of these symptoms would not eliminate the possibility of exposure, but their presence may be a good indicator of exposure.

Angiosarcoma of the liver has been identified in workers occupationally exposed to vinyl chloride. This type of tumor is extremely rare in the general population (Heath et al. 1975); therefore, its diagnosis may indicate vinyl chloride exposure. However, other causes of angiosarcoma such as exposure to arsenicals and Thorotrast (thorium dioxide; formerly used in arteriography) should be considered as possible causative factors, if present, before correlating hepatic angiosarcoma with vinyl chloride exposure (Gedigke et al. 1975; Marsteller et al. 1975). Their elimination may depend upon such factors as the magnitude of the vinyl chloride exposure and the frequency of the other causes of angiosarcoma in the population.

3.8.2 Biomarkers Used to Characterize Effects Caused by Vinyl Chloride

The realization that angiosarcoma of the liver is associated with vinyl chloride exposure prompted several investigators to try to identify assays that could be used to monitor those individuals considered to be at risk. Standard serum assays designed to detect the presence of hepatic enzymes in the blood were found to be of limited value in monitoring the progression of vinyl chloride-induced hepatic changes (Berk et al. 1975; Liss et al. 1985; Vihko et al. 1984). This may be because of the extent of hepatic damage produced by vinyl chloride and the late development of necrotic areas in the disease process (Popper et al. 1981). In contrast, studies indicate that clearance type assays, which measure liver function, are more sensitive indicators of the hepatic damage resulting from vinyl chloride exposure. These assays include the indocyanine clearance test, measurement of serum bile acids, and measurement of serum hyaluronic acid concentration (Berk et al. 1975; Liss et al. 1985; McClain et al. 2002; Vihko et al. 1984).

Liver biopsy may provide the most accurate identification of vinyl chloride-associated liver damage (Liss et al. 1985). This is because of the characteristic pattern of hepatic histopathology associated with vinyl chloride-induced damage (Popper et al. 1981). However, liver biopsy is an invasive procedure with attendant risks and, therefore, may not be justified.

Individual exposure to vinyl chloride has been linked to angiosarcoma and benign angiomatous lesions based on the monitoring of serum found to be positive for the presence of the mutant protein Asp 13 c-Ki-*ras* p21, which was not present in control individuals (DeVivo et al. 1994). Additionally, this protein was found in the serum of 49% of exposed workers who had no apparent liver lesions. It may be possible to utilize the presence of this mutant protein for the early detection of angiosarcoma of the liver.

Use of enzyme-linked immunoassay (EIA) to detect anti-p53 antibodies in serum of individuals exposed to vinyl chloride may provide an early method of screening for angiosarcoma of the liver (Trivers et al. 1995). Detection of serum anti-p53 antibodies has occurred in some, but not all, individuals exposed to vinyl chloride who later developed angiosarcoma of the liver (Trivers et al. 1995). However, not all individuals who developed angiosarcoma of the liver tested positive for anti-p53 antibodies. Also, anti-p53 antibodies are not specific to angiosarcoma of the liver but can be detected in the sera of patients with other types of cancers such as leukemia; childhood lymphoma; breast, lung, and colon cancer; and hepatocellular carcinoma.

The symptoms and signs associated with vinyl chloride disease (Raynaud's phenomenon, scleroderma-like skin changes, and acroosteolysis) are similar to those observed in systemic sclerosis. Vinyl chloride disease may be differentiated from systemic sclerosis by the absence of antinuclear antibodies in the blood and association of vinyl chloride disease with vinyl chloride exposure (Black et al. 1983, 1986). Raynaud's phenomenon is an early symptom of vinyl chloride disease. However, cyanosis and blanching of fingers with exposure to cold may be the result of a number of other conditions such as connective tissue disorders, mechanical arterial obstruction, hyperviscosity of the blood, or exposure to drugs, chemicals, or vibrating tools (Freudiger et al. 1988). Thus, other potential causes must be eliminated before this syndrome can be used to identify vinyl chloride disease. The symptoms associated with vinyl chloride disease have been attributed to vinyl chloride-induced changes in the microvasculature (Grainger et al. 1980). Capillary abnormalities in the hands may be detected using wide-field capillary microscopy and have been proposed to represent an early manifestation of the effects of vinyl chloride (Maricq et al.

1976). Also, immunofluorescent examination of biopsy material from the skin may be used to identify circulating immune complexes and their deposition on the vascular endothelium (Ward 1976).

Chromosomal aberrations found in lymphocytes may be indicative of the genotoxic effects of vinyl chloride (Anderson 2000; Anderson et al. 1980; Ducatman et al. 1975; Fucic et al. 1990, 1992; Funes-Cravioto et al. 1975; Garaj-Vrhovac et al. 1990; Hansteen et al. 1978; Hrivnak et al. 1990; Kucerova et al. 1979; Purchase et al. 1978; Sinues et al. 1991). However, any of a number of genotoxic substances can produce chromosomal aberrations. Also, de Jong et al. (1988) have found that variability in the control population may obscure the observation of chromosomal aberrations in persons exposed to low levels of vinyl chloride. G-banding analysis appeared to provide a more sensitive indication of chromosomal alteration than sister chromatid exchanges (Zhao et al. 1996). DNA damage in lymphocytes can be directly assessed using a single-cell gel electrophoresis technique. The severity of the damage may correlate with the duration of exposure (Awara et al. 1998). The DNA adducts produced by the reactive intermediary metabolites of vinyl chloride, including 1,N^6-ethenoadenosine and 3,N^4-ethenocytidine, may be more specific indicators of vinyl chloride's genotoxic potential.

3.9 INTERACTIONS WITH OTHER CHEMICALS

A number of studies have been performed that examine the effect of agents intended to alter the metabolism of vinyl chloride on its toxicity. For example, the effects of phenobarbital pretreatment on vinyl chloride-induced hepatotoxicity have been examined by Jaeger et al. (1974, 1977), Jedrychowski et al. (1985), and Reynolds et al. (1975a, 1975b). Pretreatment of rats with phenobarbital for 7 days prior to a 4-hour vinyl chloride exposure produced an increase in microsomal cytochrome P-450 activity (Reynolds et al. 1975b) and enhanced hepatotoxicity (Jaeger et al. 1974, 1977; Jedrychowski et al. 1985; Reynolds et al. 1975a, 1975b). In these studies, in the absence of the phenobarbital pretreatment, a single exposure to approximately 50,000 ppm had no detectable adverse effect on the livers of exposed rats. However, following phenobarbital pretreatment, 50,000 ppm of vinyl chloride produced increased serum activity of hepatic enzymes (Jaeger et al. 1977; Jedrychowski et al. 1985), areas of hepatic necrosis (Reynolds et al. 1975a), or both (Jaeger et al. 1974; Reynolds et al. 1975b).

Another agent known to increase MFO activity, Aroclor 1254, was also tested for its ability to enhance vinyl chloride-induced hepatotoxicity (Conolly and Jaeger 1979; Conolly et al. 1978; Jaeger et al. 1977; Reynolds et al. 1975b). Pretreatment of rats with Aroclor 1254 for several days prior to exposure to vinyl chloride resulted in an increase in serum activity of hepatic enzymes (Conolly and Jaeger 1979; Conolly

et al. 1978; Jaeger et al. 1977; Reynolds et al. 1975b) and areas of hepatic necrosis (Conolly et al. 1978; Reynolds et al. 1975b).

Additional support for a role for MFO in the enhanced toxicity of vinyl chloride was obtained using SKF525A, an MFO inhibitor. If SKF525A was administered following phenobarbital pretreatment and before vinyl chloride exposure, it blocked the ability of phenobarbital pretreatment to enhance vinyl chloride-induced hepatotoxicity (Jaeger et al. 1977).

The role of glutathione conjugation in vinyl chloride-induced toxicity was also examined (Conolly and Jaeger 1979; Jaeger et al. 1977). The investigators hypothesized that depletion of glutathione might enhance the toxicity of vinyl chloride by preventing the excretion of toxic intermediary metabolites. However, diethylmaleate, an agent known to deplete hepatic glutathione levels, had no effect on the toxicity produced by vinyl chloride following pretreatment with either phenobarbital (Jaeger et al. 1977) or Aroclor 1254 (Conolly and Jaeger 1979). Trichloropropene oxide (TCPO), another agent known to deplete hepatic glutathione, produced enhancement of the hepatic toxicity produced by Aroclor 1254 pretreatment and vinyl chloride exposure but only when the animals had been fasted prior to vinyl chloride exposure (Conolly and Jaeger 1979). The study authors hypothesized that the enhancement of vinyl chloride toxicity was a result of the ability of TCPO to inhibit epoxide hydrase rather than its ability to deplete glutathione levels. The lack of the effect of glutathione depletion indicates that the glutathione pathway is not very important at normal levels of exposure.

Although the depletion of cellular glutathione levels did not appear to enhance vinyl chloride toxicity, treatment with cysteine, the rate-limiting precursor in hepatic glutathione synthesis, increased hepatic glutathione levels and provided partial protection against the toxic effects produced by Aroclor 1254 and vinyl chloride (Conolly and Jaeger 1979).

The effects of the interaction of ethanol with vinyl chloride on development were tested by John et al. (1977). In this study, animals were exposed to vinyl chloride in the presence and absence of 15% ethanol in the drinking water during pregnancy. Ethanol produced a decrease in maternal food consumption and maternal weight gain in mice, rats, and rabbits and enhanced incidence of skeletal abnormalities in mice, and to a lesser extent, in rats. Interpretation of these results is clouded by the absence of an ethanol-exposed control group and the current recognition of the adverse effects of ethanol on pregnancy outcome.

In the experiment by Radike et al. (1981), ethanol-consuming rats exposed to vinyl chloride for a year had an enhanced incidence of hepatic angiosarcomas, hepatomas, and lymphosarcomas, earlier onset of the tumors, and an enhanced death rate. The incidence of vinyl chloride-induced angiosarcomas was potentiated by ethanol, whereas the increased incidences of hepatoma and lymphosarcomas by ethanol were additive in nature.

The effects of smoking on chromosomal aberrations in vinyl chloride-exposed workers was examined by Hrivnak et al. (1990), who found no effect of smoking in 43 workers exposed for an average of 11.2 years to levels of vinyl chloride ranging from 0.8 to 16 ppm. Most cytogenetic studies of the effects of smoking in humans have reported no effect on chromosomal aberrations, although the sister chromatid exchange frequency is usually elevated (Wong et al. 1998).

A study that examined the interaction between vinyl chloride and trichloroethylene using both inhalation exposures of rats and pharmacokinetic modeling found that trichloroethylene exposure inhibited vinyl chloride in a competitive manner (Barton et al. 1995). This interaction was observed only at high concentrations (both chemicals >10 ppm), and the study authors concluded that the interaction is not likely to be important for environmental exposures.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to vinyl chloride than will most persons exposed to the same level of vinyl chloride in the environment. Reasons may include genetic makeup, age, gender, health and nutritional status, physiological status (e.g., pregnancy), and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of vinyl chloride or compromised function of organs affected by vinyl chloride. Populations who are at greater risk due to their unusually high exposure to vinyl chloride are discussed in Section 6.7, Populations With Potentially High Exposures.

Data suggest that the following subsets of the human population may be unusually susceptible to the toxic effects of vinyl chloride: fetuses; infants; young children; people with liver disease, irregular heart rhythms, impaired peripheral circulation, or systemic sclerosis; people with exposure to organochlorine pesticides; and people consuming ethanol or barbiturates or taking Antabuse for alcoholism. Also, persons who possess the HLA-DR5, HLA-DR3, and B8 alleles may be at increased risk.

Vinyl chloride can cross the placenta and enter the blood of the fetus (Ungvary et al. 1978). Studies by Drew et al. (1983), John et al. (1977, 1981), and Maltoni et al. (1981) have shown that animals exposed by inhalation prior to adolescence or during pregnancy may have a greater death rate and increased likelihood of developing cancer than adult animals exposed for similar periods. This may relate to the length of the induction period of hepatic angiosarcoma rather than to an increased susceptibility of the young, *per se*. It is also possible that there are explanations for these findings. Cogliano and Parker (1992) suggested that in the multistage model of carcinogenesis, carcinogens that induce an initial transition early in the life of an animal would be more effective since there would be a longer period of time remaining in the lifespan for completion of the remaining transitions. Their empirical model of the effect of age at exposure on the development of cancer suggests that there is an age-sensitive period of exposure to vinyl chloride.

Vinyl chloride is metabolized in the liver in a multistep process. The intermediary metabolites of vinyl chloride, 2-chloroethylene oxide and 2-chloroacetaldehyde, have been suggested to be responsible for some of the adverse effects produced by vinyl chloride. Thus, activation of the enzyme system responsible for production of these toxic metabolites would be expected to increase the toxicity of vinyl chloride exposures. 2-Chloroethylene oxide is formed by action of the MFO system associated with cytochrome P-450. The barbiturate, phenobarbital, and the pesticide extender, Aroclor 1254, increased MFO activity and have been shown to greatly increase the hepatotoxicity of vinyl chloride (Conolly and Jaeger 1979; Conolly et al. 1978; Jaeger et al. 1974, 1977; Jedrychowski et al. 1985; Reynolds et al. 1975a, 1975b). Thus, persons taking barbiturates or who might be exposed to organochlorine pesticides that are known to induce microsomal enzymes (such as Aroclor 1254) would be expected to be at increased risk for developing vinyl chloride-induced hepatotoxicity.

Genetic polymorphisms related to vinyl chloride metabolism and DNA repair may increase the susceptibility of individuals to liver toxicity and cancer. CYP2E1 and glutathione *S*-transferase genotypes were associated with abnormal liver function, “vinyl chloride disease”, and the incidence of angiosarcoma in exposed workers (El Ghissassi et al. 1995; Green et al. 2000; Huang et al. 1997). Genotypes for CYP2E1, the DNA repair gene, x-ray repair cross-complementing group 1 (XRCC1), and aldehyde dehydrogenase 2 (ALDH2) have been associated with increased sister chromatid exchange frequency and increased expression of p53 mutant protein and anti-p53 antibody in exposed workers (Li et al. 2003; Wong et al. 1998, 2002b, 2003b). The risk of developing liver cancer also appears elevated in those with a history of Hepatitis B viral infection (Du and Wang 1998; Wong et al. 2003b).

Radike et al. (1981) demonstrated that ethanol-consuming rats exposed to vinyl chloride had an increased incidence of cancer and an earlier death rate than animals exposed to vinyl chloride in the absence of ethanol.

Some persons consume the agent, Antabuse, to curb the desire for alcohol. In its role as a therapeutic agent, Antabuse blocks aldehyde dehydrogenase and causes a build-up of acetaldehyde, which is emetic, in the body when alcohol is consumed. If persons taking Antabuse are exposed to vinyl chloride, the alternative metabolic pathway for vinyl chloride metabolism will be blocked, causing more vinyl chloride to be metabolized to the toxic metabolite, 2-chloroethylene oxide. Thus, these persons may be at increased risk for hepatotoxicity, cancer, and death at an early age.

Very high levels of vinyl chloride have been demonstrated to cause cardiac arrhythmias in dogs (Carr et al. 1949; Oster et al. 1947). Persons with a propensity to develop cardiac arrhythmias because of heart disease or damage may be at an increased risk of having heart beat irregularities when exposed to high concentrations of vinyl chloride.

Vinyl chloride has been shown to produce decreased circulation in the hands and fingers of some people. Persons with impaired circulation due to some other cause such as connective tissue disorders, systemic sclerosis, hyperviscosity of the blood, or use of vibrating tools, may experience more severe impairment of the circulation.

Work by Black et al. (1983, 1986) has shown that persons with the HLA allele HLA-DR5 may have an increased likelihood of developing vinyl chloride disease, and those with the alleles HLA-DR3 and B8 may have an increased severity of the disease.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to vinyl chloride. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to vinyl chloride. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted

for medical advice. The following texts provide specific information about treatment following exposures to vinyl chloride:

Bronstein AC, Currance PL, eds. 1988. Emergency care for hazardous materials exposure. St. Louis, MO: CV Mosby Company, 143-144.

Haddad LM, Winchester JF, eds. 1990. Clinical management of poisoning and overdose. Philadelphia, PA: W.B. Saunders Company, 516, 1209, 1214, 1224, 1227-1229.

Stutz DR, Ulin S, eds. 1992. Hazardous materials injuries. A handbook for pre-hospital care. 3rd ed. Beltsville, MD: Bradford Communications Corporation, 286-287.

3.11.1 Reducing Peak Absorption Following Exposure

Limited information from humans and results from animal studies indicate that vinyl chloride is rapidly and virtually completely absorbed following inhalation and oral exposure, but animal studies suggest that dermal absorption of vinyl chloride gas is not likely to be significant (see Section 3.3.1). Efforts to reduce absorption following acute exposure to vinyl chloride should focus on removing the individual from the site of exposure and decontaminating exposed areas of the body. Vinyl chloride gas is relatively dense and accumulates at ground level. Therefore, the subject should be moved from low-lying areas. Contaminated skin may be washed with soap and water; however, this will most likely not prevent tissue damage produced by frostbite from the cooling caused by the rapid evaporation of vinyl chloride from the skin. It is suggested that eyes exposed to vinyl chloride be copiously irrigated with water or normal saline (Bronstein and Currance 1988; Haddad and Winchester 1990; Stutz and Ulin 1992). Because of its volatility, it is unlikely that vinyl chloride would be ingested unless it had been dissolved in a solvent. If such ingestion of vinyl chloride occurs, it is suggested that water or milk be administered for dilution if the patient can swallow, has a good gag reflex, and is not drooling (Bronstein and Currance 1988; Stutz and Ulin 1992). In addition, gastric lavage and administration of activated charcoal have been suggested as a means to reduce absorption of vinyl chloride. Induction of emesis is contraindicated (Bronstein and Currance 1988; Haddad and Winchester 1990; Stutz and Ulin 1992).

3.11.2 Reducing Body Burden

Because of its rapid metabolism and excretion, vinyl chloride does not tend to accumulate in the body. As discussed in Section 3.4.3, the metabolism of vinyl chloride is a dose-dependent, saturable process. Vinyl chloride is oxidized primarily by the microsomal MFO system (cytochrome P-450) to a reactive

epoxide intermediate (2-chloroethylene oxide), which can rearrange to 2-chloroacetaldehyde or conjugate with glutathione to form *S*-formylmethyl glutathione. At exposure concentrations below about 1,000 ppm in air, very little vinyl chloride is excreted unchanged in the exhaled air. However, when metabolic saturation occurs at high exposure concentrations (approximately 1,000 ppm following inhalation exposure in rats [Watanabe and Gehring 1976; Watanabe et al. 1976b] and approximately 20 mg/kg following oral administration to rats [Green and Hathway 1975; Watanabe and Gehring 1976; Watanabe et al. 1976a]), vinyl chloride is excreted unchanged in expired air. Therefore, a possible means to enhance the elimination of vinyl chloride without allowing its biotransformation to toxic intermediates is to saturate this oxidative pathway by administration of substances known to be metabolized via this route. Saturation of the P-450 system may occur with drugs such as phenytoin or dicumerol (Goodman and Gilman 1980). However, the effectiveness of these agents in blocking the P-450 metabolism of vinyl chloride has not been tested, and it is unclear whether toxic doses would be necessary to overcome the relative affinities of the enzymes for vinyl chloride versus these agents. In addition, the potential toxicity of any side products of these substances would need to be considered in any protocol. Several agents induce activity of the microsomal enzymes and could potentially increase the toxicity of vinyl chloride. Administration of such substances would be contraindicated.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Following acute, high-level exposure, vinyl chloride behaves as an anesthetic and produces central nervous system and respiratory depression (see Sections 3.2.1.4). Therefore, basic life support measures, such as supplemental oxygen and cardiopulmonary resuscitation, are suggested in such instances (Bronstein and Currance 1988; Haddad and Winchester 1990; Stutz and Ulin 1992). In addition, like other halogenated hydrocarbons, vinyl chloride may sensitize the heart to the effects of circulating catecholamines. Therefore, the patient's cardiac rhythm should be monitored, and the use of isoproterenol, epinephrine, or other sympathomimetic drugs should be avoided (Haddad and Winchester 1990).

Vinyl chloride is a known human and animal carcinogen; long-term exposure to this compound is associated with an increased incidence of hepatic angiosarcomas (see Section 3.2.1.7). Vinyl chloride is also hepatotoxic. The mechanism by which vinyl chloride induces its carcinogenic and toxic effect on the liver has been well studied. A reactive epoxide intermediate of vinyl chloride, 2-chloroethylene oxide, interacts directly with DNA and RNA producing cyclic etheno-adducts that include 1,N^6-ethenoadenine, 3,N^4-ethenocytosine, N^2,3-ethenoguanine, and 1,N^2-ethenoguanine. This alkylation results in highly

efficient base-pair substitution, leading to neoplastic transformation (see Section 3.5.2). As discussed above, this epoxide intermediate is formed when vinyl chloride is oxidized by the P-450 isoenzymes. Interference with this metabolic pathway, therefore, could reduce the toxic and carcinogenic effects of vinyl chloride by reducing the amount of epoxide produced. A number of drugs, such a cobaltous chloride, SKF-535-A, and 6-nitro-1,2,3-benzothioadiazole, have been reported to inhibit P-450 enzymes. Pretreatment with 6-nitro-1,2,3-benzothioadiazole completely blocked the metabolism of vinyl chloride in rats exposed to 0.45 ppm in a closed system for 5 hours (Bolt et al. 1977). P-450 metabolism also results in products that can be more readily eliminated than can the parent compound. Hence, any side products of the drugs and their potential to increase the biological half-life of vinyl chloride would also need to be considered in any protocol. In fact, a study by Buchter et al. (1977) showed that substantial unmetabolized vinyl chloride accumulated in fatty tissue when 6-nitro-1,2,3-benzothioadiazole was used to block P-450 metabolism. The study did not examine the fate of vinyl chloride in fatty tissue after P-450 metabolism was reactivated, but it is likely that vinyl chloride would leave the fat slowly and be metabolized. Thus, while P-450 metabolism would probably reduce the generation of toxic metabolites in the short term, it is unclear whether the generation of toxic metabolites could be completely avoided. Further research to determine which isozymes are involved in the metabolism to the reactive intermediates, as well as which isozymes are involved in enhancing the elimination of vinyl chloride, could lead to the development of strategies to selectively inhibit specific isozymes and thus reduce the toxic effects of vinyl chloride.

Because vinyl chloride is detoxified by conjugation with glutathione and/or cysteine (see discussion above and Section 3.4.3), ensuring sufficient glutathione stores in the body (e.g., by treatment with *N*-acetyl cysteine) may reduce the possibility of toxic effects following acute exposure to vinyl chloride.

Vinyl chloride disease has been reported in a small percentage of workers exposed to this compound. One of the symptoms of this condition is Raynaud's phenomenon (blanching, numbness, and discomfort of the fingers upon exposure to cold). Studies of these individuals demonstrated that vinyl chloride may produce blockage of the blood vessels supplying the hand, hypervascularity, and a thickening of the blood vessel walls (Harris and Adams 1967; Preston et al. 1976; Veltman et al. 1975; Walker 1976). Several investigators have suggested that the mechanism for vinyl chloride disease may be an autoimmune response similar to systemic sclerosis. Grainger et al. (1980) and Ward (1976) proposed that a reactive vinyl chloride intermediate metabolite, such as 2-chloroethylene oxide or 2-chloroacetaldehyde, binds to a protein such as IgG. The altered protein initiates an immune response, with deposition of immune products along the vascular endothelium. Cold temperatures could produce the precipitation of these

immune complexes resulting in blockage of the blood vessels. Another characteristic of vinyl chloride disease is acroosteolysis, in which the terminal phalanges of the fingers are resorbed. This condition has been noted predominantly in workers who first had Raynaud's phenomenon (Dinman et al. 1971; Freudiger et al. 1988; Harris and Adams 1967; Magnavita et al. 1986; Markowitz et al. 1972; Preston et al. 1976; Sakabe 1975; Veltman et al. 1975; Wilson et al. 1967). The resorptive bone changes may be due to activation of osteoclasts secondary to vascular insufficiency in the finger tips, but this remains to be demonstrated conclusively. Other manifestations of vinyl chloride disease include joint and muscle pain, enhanced collagen deposition, stiffness of the hands, and scleroderma-like skin changes. Increased levels of circulating immune complexes and immunoglobulins have been observed in vinyl chloride workers, suggesting a stimulatory effect of vinyl chloride on the immune system (Bogdanikowa and Zawilska 1984). A correlation between the severity of the symptoms of vinyl chloride disease and the magnitude of the immune response was observed (Grainger et al. 1980; Langauer-Lewowicka et al. 1976; Ward 1976). Research on the genetic characteristics of workers with this disease has demonstrated that the susceptibility to vinyl chloride disease was increased in the presence of the HLA-DR5 allele or a gene in linkage disequilibrium with it, and progression of the disease to its more severe forms was favored by HLA-DR3 and B8 (Black et al. 1983, 1986). If vinyl chloride disease is mediated by an immune mechanism in individuals with a genetic predisposition, then the effects of this disease may be mitigated by administration of drugs used to treat other similar autoimmune diseases (e.g., azathioprine, cyclophosphamide, and prednisone). However, the toxicity associated with the use of these drugs must also be considered.

3.12 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the adverse health effects of vinyl chloride is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to ensure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such adverse health effects) of vinyl chloride.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean

that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

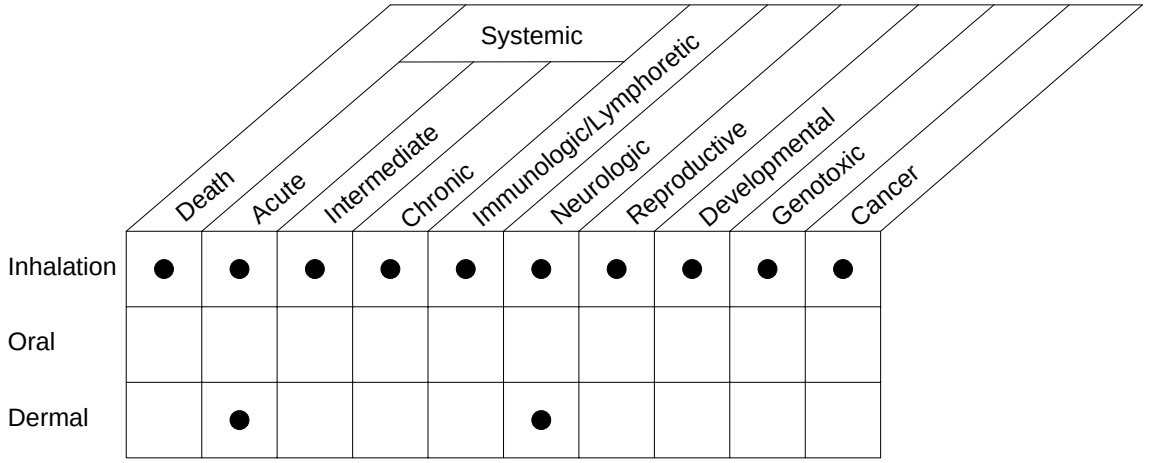
3.12.1 Existing Information on Adverse Health Effects of Vinyl Chloride

The existing data on the adverse health effects of inhalation, oral, and dermal exposure of humans and animals to vinyl chloride are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the adverse health effects of vinyl chloride. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

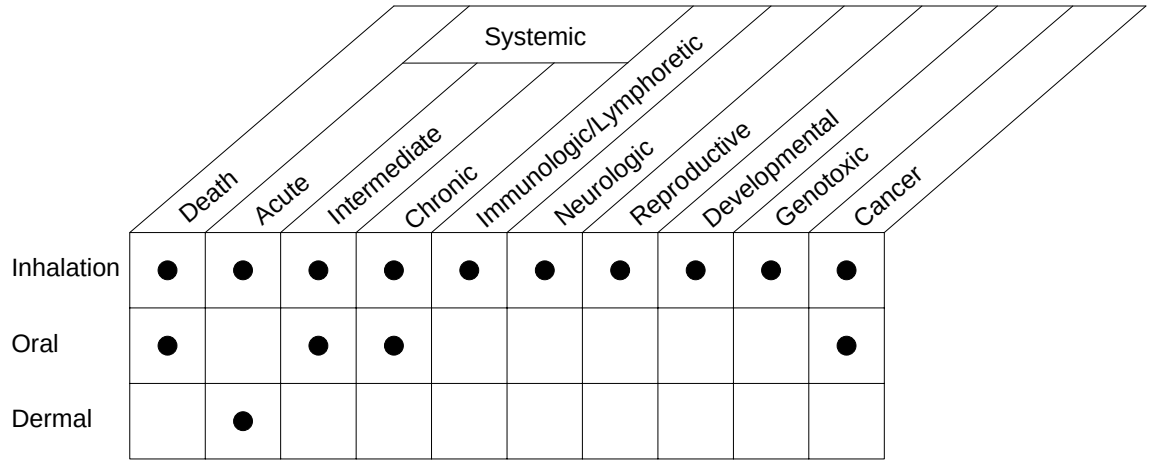
Virtually all of the literature regarding adverse health effects in humans comes from studies of workers exposed to vinyl chloride during the production of PVC. Case reports and cohort studies describe some acute health effects and a wide range of long-term health effects. The predominant mode of exposure in these studies is via inhalation. These studies are limited by the lack of reliable data on individual exposure levels. No studies were found regarding the adverse health effects of oral exposure. One case report examined the effects of dermal exposure to liquid vinyl chloride, but exposure by this route is not expected to contribute significantly to producing adverse health effects because of the limited absorption of vinyl chloride through the skin.

A large number of studies examining the adverse health effects of inhaled vinyl chloride in animals were reviewed. As can be seen in Figure 3-5, no information is available on acute adverse systemic effects, immunologic, neurologic, reproductive, developmental, or genotoxic effects of exposure of animals by the oral route. One study examined the effects of dermal/ocular exposure to vinyl chloride gas, but toxicokinetic studies indicate that this route is not an important means of exposure.

Figure 3-5. Existing Information on Health Effects of Vinyl Chloride



Human



Animal

● Existing Studies

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Populations in areas that contain hazardous waste sites may be exposed to vinyl chloride for brief periods. Exposure most likely would occur by inhalation, but relatively brief oral and dermal exposures are also possible. There are acute inhalation exposure data in humans and animals that indicate that the central nervous system is a major target organ of vinyl chloride toxicity.

Symptoms of central nervous system depression ranging from dizziness and drowsiness to loss of consciousness have been observed in humans and animals as a result of brief exposure to very high levels of vinyl chloride (Hehir et al. 1981; Jaeger et al. 1974; Lester et al. 1963; Mastromatteo et al. 1960; Patty et al. 1930). A threshold for central nervous system effects appears to be approximately 8,000 ppm (Lester et al. 1963). Extremely high concentrations of vinyl chloride produce respiratory irritation and death in humans and animals by the inhalation route (Danziger 1960; Lester et al. 1963; Mastromatteo et al. 1960; Patty et al. 1930). Based on studies in animals, the threshold for these effects appears to be in the range of 100,000–400,000 ppm (Lester et al. 1963; Mastromatteo et al. 1960; Patty et al. 1930). However, increased rate of death was noted in pregnant mice at 500 ppm (John et al. 1977, 1981). Extremely high concentrations of vinyl chloride produced cardiac arrhythmias in dogs exposed by the inhalation route (Carr et al. 1949; Oster et al. 1947). Although no threshold was reported for these effects, concentrations of this magnitude would not likely be encountered by humans. Pharmacokinetic data indicate that similar end points might be expected if sufficiently high doses could be consumed by the oral route. However, the solubility characteristics of vinyl chloride in aqueous media (1,100–2,763 mg/L at 25 °C) (Cowfer and Magistro 1983; EPA 1985b) indicate that achieving concentrations of vinyl chloride in excess of 5,000 ppm may be extremely difficult. Animal studies indicate that acute inhalation exposures to vinyl chloride can produce developmental effects at concentrations that also cause significant maternal toxicity (John et al. 1977, 1981; Ungvary et al. 1978). Concentrations of 500 ppm were observed to produce delayed ossification in the fetus and decreased food consumption, body weight gain, and increased rate of mortality in maternal mice (John et al. 1977, 1981). The NOAEL (50 ppm) in this study was used to derive an acute-duration inhalation MRL. Animal studies examining the developmental, neurological, and systemic effects of the highest doses achievable in drinking water would be helpful for determining whether any effects would occur when vinyl chloride-contaminated groundwater or food products are consumed. One report described severe frostbite with second degree burns on the hands of a man resulting from the rapid evaporation of spilled liquid vinyl chloride (Harris 1953). A toxicokinetic study using two monkeys indicates that absorption of vinyl chloride by the dermal route is exceedingly small (Hefner et al. 1975a); thus, studies examining the effects of acute-duration

dermal exposure do not seem warranted. However, if further toxicokinetics studies contradict these findings, acute-duration dermal exposure studies in animals may be valuable.

A report was located regarding adverse hepatic and respiratory effects observed 18 months following a single 1-hour inhalation exposure to vinyl chloride (Hehir et al. 1981). However, limitations in the study diminished its reliability. Because of the implications of adverse chronic effects from acute exposure, confirmation of these results in another study would be valuable.

Intermediate-Duration Exposure. No studies in humans specifically address intermediate-duration effects by any route. Most epidemiological studies of occupationally exposed persons have concentrated on persons who have been employed over several years. A study with reliable quantification of exposure levels that examined the effects experienced by vinyl chloride workers in their first year of exposure would be helpful for predicting the effects that might be observed in populations exposed to hazardous waste sites for similar periods of time. However, at current low levels of exposure in the workplace, it may be difficult to demonstrate effects. There is a large database describing the effects of intermediate-duration inhalation exposures in animals (Adkins et al. 1986; Bi et al. 1985; Drew et al. 1983; Du et al. 1979; Feron et al. 1979a, 1979b; Hong et al. 1981; Lee et al. 1978; Lester et al. 1963; Maltoni et al. 1981; Mirkova et al. 1978; Sal'nikova and Kotsovskaya 1980; Schaffner 1978; Sharma and Gehring 1979; Short et al. 1977; Sokal et al. 1980; Suzuki 1978, 1981; Thornton et al. 2002; Torkelson et al. 1961; Wisniewska-Knypl et al. 1980). Animals exposed to vinyl chloride for more than 2 weeks and less than a year have experienced effects on the liver, kidneys, lungs, and blood (Bi et al. 1985; Du et al. 1979; Feron et al. 1979a, 1979b; Lester et al. 1963; Sal'nikova and Kotsovskaya 1980; Schaffner 1978; Sokal et al. 1980; Torkelson et al. 1961; Wisniewska-Knypl et al. 1980). Data were sufficient to determine an intermediate-duration inhalation MRL based on adverse liver effects in rats. The MRL was based on a NOAEL of 15 ppm for hepatic centrilobular hypertrophy (Thornton et al. 2002). Extremely limited information was available regarding oral intermediate-duration effects. One chronic study presented interim sacrifice data that identified relative weight and histopathological changes in the liver (Feron et al. 1981). However, only a single-dose group was compared to controls, precluding determination of the dose-response of the effects observed. Thus, no MRL for oral intermediate-duration exposures could be determined. Additional studies examining the effects of oral exposure to vinyl chloride would be helpful for evaluating relevant biomarkers of exposure and effects in humans consuming contaminated drinking water or foods (see Section 3.8). As noted above, absorption of vinyl chloride through the skin is not expected to be significant (Hefner et al. 1975a); thus, additional dermal exposure studies do not seem

warranted. However, if further toxicokinetics studies contradict these findings, other intermediate-duration dermal exposure studies may be valuable.

Chronic-Duration Exposure and Cancer. A large number of studies of workers exposed to vinyl chloride have identified a wide range of target organs that may be affected by chronic-duration inhalation of vinyl chloride (Bao et al. 1988; Bencko et al. 1988; Berk et al. 1975; Black et al. 1983, 1986; Bogdanikowa and Zawilska 1984; Brugnami et al. 1988; Byren et al. 1976; Creech and Johnson 1974; Dinman et al. 1971; Falk et al. 1974; Freudiger et al. 1988; Fucic et al. 1995; Gedigke et al. 1975; Grainger et al. 1980; Harris and Adams 1967; Jayson et al. 1976; Jones and Smith 1982; Langauer-Lewowicka et al. 1976; Laplanche et al. 1987; Lee et al. 1977b; Lilis et al. 1975; Liss et al. 1985; Lloyd et al. 1984; Magnavita et al. 1986; Maricq et al. 1976; Markowitz et al. 1972; Marsteller et al. 1975; Micu et al. 1985; Miller 1975; NIOSH 1977; Perticoni et al. 1986; Popper and Thomas 1975; Popper et al. 1981; Preston et al. 1976; Sakabe 1975; Spirtas et al. 1975; Suciu et al. 1963, 1975; Tamburro et al. 1984; Veltman et al. 1975; Vihko et al. 1984; Walker 1976; Ward 1976; Wilson et al. 1967; Wong et al. 1991). The target organs include the liver, lungs, blood, immune system, cardiovascular system, skin, bones, nervous system, and the reproductive organs. These studies are severely limited in that individual exposure levels have not been documented. In general, studies in animals provide supportive evidence for these effects and give indications of the exposure levels that may be associated with them (Bi et al. 1985; Feron and Kroes 1979; Feron et al. 1979a, 1979b; Lee et al. 1981; Thornton et al. 2002; Viola 1970; Viola et al. 1971).

No information was available regarding chronic-duration oral exposure in humans. However, studies in animals indicate that the liver, blood, and skin are target organs for oral exposure to vinyl chloride (Feron et al. 1981; Knight and Gibbons 1987; Til et al. 1983, 1991). A chronic-duration oral MRL of 0.003 mg/kg/day was derived from a human equivalent NOAEL of 0.09 mg/kg/day based on liver cell polymorphism in rats (Til et al. 1983, 1991).

No information was available regarding effects of chronic-duration dermal exposure in humans or animals, but absorption of vinyl chloride gas through the skin was not significant in an acute-duration exposure study in monkeys (Hefner et al. 1975a). However, only two animals were used, and this was the only study located that examined toxicokinetics after dermal exposure. No information is available regarding dermal absorption of vinyl chloride from liquid or solid media (i.e., water, soil). Dermal exposure from these media is expected to be minimal; however, a study confirming this assumption

would be useful. If further toxicokinetic studies demonstrate significant dermal absorption of vinyl chloride, then other intermediate-duration dermal exposure studies may be needed.

There is sufficient evidence to indicate that vinyl chloride is carcinogenic to humans (Belli et al. 1987; Boffetta et al. 2003; Brugnami et al. 1988; Byren et al. 1976; Cheng et al. 1999; Chung and Keh 1987; Cooper 1981; Creech and Johnson 1974; Davies et al. 1990; Du and Wang 1998; Fitzgerald and Griffiths 1987; Fox and Collier 1977; Gelin et al. 1989; Geryk and Zudova 1986; Hagmar et al. 1990; Heldass et al. 1987; Infante et al. 1976b; Jones et al. 1988; Lelbach 1996; Lewis 2001; Lewis and Rempala 2003; Lewis et al. 2003; Monson et al. 1975; Mundt et al. 2000; Ojajarvi et al. 2001; Pirastu et al. 1990; Rhomberg 1998; Rinsky et al. 1988; Saurin et al. 1997; Simonato et al. 1991; Smulevich et al. 1988; Teta et al. 1990; Ward et al. 2001; Waxweiler et al. 1981; Weber et al. 1981; Weihrauch et al. 2000; Williamson and Ramsden 1988; Wong et al. 1991, 2002a, 2002b, 2003a, 2003b; Wu et al. 1989) and animals (Bi et al. 1985; Drew et al. 1983; Feron and Kroes 1979; Feron et al. 1979a; Froment et al. 1994; Lee et al. 1978; Maltoni et al. 1981; Viola et al. 1971) exposed via inhalation, and in animals exposed via the oral route (Feron et al. 1979a; Maltoni et al. 1981; Til et al. 1983, 1991). The mechanism for carcinogenicity appears to be associated with the formation of reactive intermediates that bind to DNA.

Genotoxicity. There are substantial data on clastogenesis in humans exposed to vinyl chloride that indicate that this chemical acts as a potent genotoxicant (Anderson 2000; Anderson et al. 1980; Awara et al. 1998; Becker et al. 2001; Ducatman et al. 1975; Fucic et al. 1990, 1992, 1995; Funes-Cravioto et al. 1975; Hansteen et al. 1978; Hrivnak et al. 1990; Huttner and Nikolova 1998; Huttner et al. 1998, 1999; Kucerova et al. 1979; Marion et al. 1991; Purchase et al. 1978; Sinues et al. 1991; Wong et al. 1998; Zhao et al. 1996). The reversibility of chromosome damage has been reported for several populations of workers following a cessation or reduction of exposure to vinyl chloride (Anderson et al. 1980; Fucic et al. 1996a, 1996b; Hansteen et al. 1978). Findings in humans are supported by both animal studies and *in vitro* studies that show positive genotoxicity in a variety of microbial organisms, cultured cell lines, and isolated nucleic acid assays (Anderson and Richardson 1981; Andrews et al. 1976; Bartsch 1976; Bartsch et al. 1976; Bolt et al. 1986; Ciroussel et al. 1990; de Meester et al. 1980; Eberle et al. 1989; Froment et al. 1994; Green and Hathway 1978; Gwinner et al. 1983; Hansteen et al. 1978; Huberman et al. 1975; Jacobsen et al. 1989; Kandala et al. 1990; Laib and Bolt 1977; Laib et al. 1989; Loprieno et al. 1977; McCann et al. 1975; Osterman-Golkar et al. 1977; Poncelet et al. 1980; Rannug et al. 1974, 1976; Simmon et al. 1977; Singer et al. 1987; Victorin and Stahlberg 1988a; Walles et al. 1988). The role of etheno-adducts in the carcinogenesis of vinyl chloride has been extensively studied (Albertini et al. 2003, Barbin 1998, 1999, 2000; Kielhorn et al. 2000; Nivard and Vogel 1999; Whysner et al. 1996). Both

2-chloroethylene oxide and 2-chloroacetaldehyde can react with DNA nucleotide bases; however, 2-chloroethylene oxide is a more potent mutagen and may be the ultimate carcinogenic metabolite of vinyl chloride (Chiang et al. 1997). Etheno-adducts generate mainly base pair substitution mutations. Mutations in specific genes (i.e., *ras* oncogenes, p53 tumor suppressor gene) have been identified in vinyl chloride-induced liver tumors in rats and humans (Barbin et al. 1997; Brandt-Rauf et al. 1995; Hollstein et al. 1994; Marion and Boivin-Angele 1999; Marion et al. 1991; Trivers et al. 1995; Weihrauch et al. 2002). Immunological techniques have been used to detect the presence of Asp13p21 (oncoprotein for mutation of the Ki-*ras* gene), p53 mutant protein, and p53 antibodies in the serum of exposed workers (Brandt-Rauf et al. 2000a, 2000b; Marion 1998). Statistical analyses suggest a relationship between vinyl chloride exposure and the presence of these serum biomarkers; however, the predictive value of these biomarkers for development of cancer is not known. Further mechanistic research would be helpful in identifying the specific gene mutations responsible for vinyl chloride-induced liver cancer.

Reproductive Toxicity. Data from a number of epidemiological studies provide suggestive evidence of adverse effects on male and female reproductive function. Sexual impotence and decreased androgen levels were found in men exposed occupationally to vinyl chloride (Suciu et al. 1975; Veltman et al. 1975; Walker 1976). In women exposed to vinyl chloride, menstrual disturbances and an increased incidence of elevated blood pressure and edema during pregnancy (preeclampsia) were observed (Bao et al. 1988). Animal studies indicate that exposure to vinyl chloride can result in a decrease in testicular weight, damage to the seminiferous tubules, and depletion of spermatocytes (Bi et al. 1985). A significant increase in damage to the spermatogenic epithelium and disorders of spermatogenesis were also observed (Sokal et al. 1980). Reproductive capability was not affected in a 2-generation inhalation reproductive toxicity study in rats (Thornton et al. 2002). No effects were seen in body weight, feed consumption, ability to reproduce, gestation index or length, or pre- and postweaning developmental landmarks. Sperm counts, motility, and morphology were also unaffected by vinyl chloride exposure. Animal models of preeclampsia could be tested to determine the mechanism by which vinyl chloride might produce this effect. Well-designed and well-conducted epidemiological studies examining such changes would also be helpful. No data are available on the possible reproductive toxicity resulting from oral exposure to vinyl chloride. Oral studies that use drinking water as the vehicle of administration would be particularly useful because contaminated groundwater is a potentially significant source of human exposure. However, such studies would be technically difficult to perform due to the volatility of vinyl chloride and its low solubility in water. The PBPK model would be useful for assessing reproductive toxicity resulting from oral exposure to vinyl chloride.

Developmental Toxicity. The epidemiological studies that have addressed developmental toxicity in offspring of humans who have been exposed to vinyl chloride are controversial. Although some of these purport to show a significant association between birth defects and vinyl chloride exposure (Infante 1976; Infante et al. 1976a, 1976b; NIOSH 1977), their design and analysis have been severely criticized (Hatch et al. 1981; Stallones 1987). At this time, there are insufficient human data to provide a definitive answer to this question. A well-designed and well-conducted epidemiological study examining potential developmental end points would be helpful. There are also inconsistencies in the developmental toxicity data for vinyl chloride in laboratory animals. In general, vinyl chloride produced minor adverse developmental effects only at concentrations that were significantly toxic to maternal animals. Concentrations of 500 ppm were observed to produce delayed ossification in the fetus and decreased food consumption, body weight gain, and mortality in maternal mice (John et al. 1977, 1981). In contrast, no adverse effects were reported in an embryo-fetal developmental toxicity study conducted in rats exposed to vinyl chloride via inhalation (Thornton et al. 2002). Embryo-fetal developmental parameters including uterine implantation, fetal gender distribution, fetal body weight, and fetal malformations and variations were not affected by vinyl chloride exposure. Vinyl chloride produced a decrease in maternal body weight gain at all exposure levels; however, no changes were observed in feed consumption, clinical signs, or postmortem gross findings. Maternal liver and kidney weights were increased relative to total body weight. It would be helpful to determine whether pregnancy increases the susceptibility to vinyl chloride in the mother. There are no data for oral exposures. Because of this deficiency, oral studies examining a range of developmental end points would be useful in assessing the possibility of these effects in humans. However, such studies would be technically difficult to perform due to the volatility of vinyl chloride and its low solubility in water. The PBPK model would be a useful tool in such risk assessment.

Immunotoxicity. Studies of workers occupationally exposed to vinyl chloride suggest that the immune system may be activated by vinyl chloride (Bogdanikowa and Zawilska 1984). Some data suggest that reactive intermediates may bind to proteins in the body, sufficiently altering them so that they become antigenic (Grainger et al. 1980). In some instances, an autoimmune-like syndrome develops. The likelihood of this may be associated with the possession by individuals of specific genetic determinants (HLA alleles) (Black et al. 1983, 1986). Because of the low incidence of the autoimmune response in humans, the immunotoxicity may be best further studied in one of the strains of mice known to have a propensity for developing autoimmune diseases. Also, additional epidemiological studies examining the immune response of exposed populations may be helpful.

Neurotoxicity. A number of studies in humans (Lester et al. 1963; Patty et al. 1930) and animals (Hehir et al. 1981; Jaeger et al. 1974; Lester et al. 1963; Mastromatteo et al. 1960; Patty et al. 1930) demonstrate that vinyl chloride is a central nervous system depressant following brief high-level inhalation exposures. Two studies in animals have also found degenerative effects in central nervous system tissue following chronic inhalation exposure to high levels of vinyl chloride (Viola 1970; Viola et al. 1971). It is unknown whether these degenerative changes might also occur at lower doses; thus, a study examining the effects of a range of lower doses would be informative. In addition, relatively recent studies present suggestive evidence that vinyl chloride may also produce peripheral nerve damage in humans exposed chronically via inhalation (Langauer-Lewowicka et al. 1976; Magnavita et al. 1986; Perticoni et al. 1986; Sakabe 1975; Walker 1976). Animal studies examining histopathological and electrophysiological end points in peripheral nerves would be helpful for assessing what doses may be associated with this effect. Epidemiological studies examining exposed populations for subclinical peripheral nerve damage would also be helpful.

Epidemiological and Human Dosimetry Studies. Virtually all of the data on effects in humans following inhalation exposure to vinyl chloride come from epidemiological studies of workers exposed during the production of PVC (Belli et al. 1987; Boffetta et al. 2003; Brugnami et al. 1988; Byren et al. 1976; Cheng et al. 1999; Chung and Keh 1987; Cooper 1981; Creech and Johnson 1974; Davies et al. 1990; Du and Wang 1998; Fitzgerald and Griffiths 1987; Fox and Collier 1977; Gelin et al. 1989; Geryk and Zudova 1986; Hagmar et al. 1990; Heldass et al. 1987; Infante et al. 1976b; Jones et al. 1988; Lelbach 1996; Lewis 2001; Lewis and Rempala 2003; Lewis et al. 2003; Monson et al. 1975; Mundt et al. 2000; Ojajarvi et al. 2001; Pirastu et al. 1990; Rhomberg 1998; Rinsky et al. 1988; Saurin et al. 1997; Simonato et al. 1991; Smulevich et al. 1988; Teta et al. 1990; Ward et al. 2001; Waxweiler et al. 1981; Weber et al. 1981; Weihrauch et al. 2000; Williamson and Ramsden 1988; Wong et al. 2002a, 2002b, 2003a, 2003b, 1991; Wu et al. 1989). These studies are limited by the absence of information on individual exposure levels. Also, in North America and Western Europe, only limited numbers of females have been studied.

For the most part, studies examining the carcinogenic potential of vinyl chloride have been adequate to distinguish an increased incidence of the rare cancer, angiosarcoma (Byren et al. 1976; Creech and Johnson 1974; Fox and Collier 1977; Infante et al. 1976b; Jones et al. 1988; Monson et al. 1975; Pirastu et al. 1990; Rinsky et al. 1988; Teta et al. 1990; Waxweiler et al. 1976; Weber et al. 1981; Wong et al. 1991; Wu et al. 1989). However, many studies have used cohorts that are too small to detect smaller increases in other types of cancer (respiratory, central nervous system, lymphatic, or hematopoietic).

Epidemiological studies designed to investigate reproductive and developmental effects of vinyl chloride have not been useful, in part because of a poor choice of statistical analysis, inadequate controls, lack of effects due to current low levels of exposure, or failure to take into account nutritional status and other chemical exposures. Additional cohort studies of these end points would be useful for examining these effects in humans.

Clastogenic effects have been used as a dosimeter for exposures to radioactive substances, and work has been done to use this approach for chemical exposures as well. More data on quantified exposures and well-controlled cytogenetic studies would be useful in developing a method for monitoring populations living near hazardous waste sites.

Biomarkers of Exposure and Effect.

Exposure. Several potential biomarkers for exposure to vinyl chloride have been identified. Vinyl chloride measured in expired air is an adequate indicator of recent, moderate-to-high-level exposure (Baretta et al. 1969). However, for low-level exposures or exposures that occur over 1–2 hours prior to the time of measurement, this biomarker is not useful. Thiodiglycolic acid, a major urinary metabolite of vinyl chloride, has been used to monitor workers occupationally exposed to vinyl chloride (Müller et al. 1979). However, this biomarker is rapidly excreted, and therefore, the period of its utility is limited (Watanabe and Gehring 1976; Watanabe et al. 1979b). Also, thiodiglycolic acid is not specific for vinyl chloride; it may also be produced as a result of the metabolism of 1,1-dichloroethene, ethylene oxide, or 2,2-dichloroethylether (Norpoth et al. 1986; Pettit 1986).

The DNA adducts 1,N^6-ethenoadenosine and 3,N^4-ethenocytidine may be used to indicate vinyl chloride exposure, although studies correlating the levels of these adducts with exposure levels are still lacking. These products remain in the body longer than free vinyl chloride or thiodiglycolic acid, thereby increasing the period after exposure that a potential exposure may be detected (Bolt 1986; Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1987a, 1987b). However, the presence of these adducts cannot indicate how long it has been since exposure occurred. In addition, these adducts are formed as the result of binding of the intermediary metabolites with nucleic acids, and other compounds producing the same intermediary metabolites will also produce these adducts. For example, these adducts have been identified as a result of exposure to vinyl bromide, ethyl carbamate, acrylonitrile, 2-cyanoethylene, and 1,2-dichloroethane (Bolt et al. 1986; Svensson and Osterman-Golkar 1986). Studies attempting to identify a metabolite more specific to vinyl chloride may be helpful in

developing a biomarker that may be used to facilitate future medical surveillance, which can lead to early detection and possible treatment.

Vinyl chloride-induced genetic alterations have been identified in the Ki-*ras* oncogene and the p53 tumor suppressor gene, and oncoproteins and p53 antibodies have been detected in the serum of cancer patients with angiosarcoma (see Section 3.3). Immunological techniques have been used to detect the presence of Asp13p21 (oncoprotein for mutation of the Ki-*ras* gene), p53 mutant protein, and p53 antibodies in the serum of exposed workers (Brandt-Rauf et al. 2000a, 2000b; Marion 1998). Statistical analyses suggest a relationship between vinyl chloride exposure and the presence of these serum biomarkers; however, the predictive value of these biomarkers for development of cancer is not known.

Effect. With regard to biomarkers of effect of vinyl chloride exposure, numerous indicators have been examined. The central nervous system depression associated with brief high-level exposures is easily determined by observation. The hepatic changes that may develop during longer term exposures are difficult to detect by standard biochemical liver function tests (Berk et al. 1975; Du et al. 1995; Liss et al. 1985; Vihko et al. 1984). In contrast, tests of clearance such as the indocyanine clearance test or measurement of serum bile acid levels are more specific and sensitive indicators of vinyl chloride-induced liver damage (Berk et al. 1975; Liss et al. 1985; Vihko et al. 1984). Angiosarcoma of the liver is a rare tumor type that has been shown to result from vinyl chloride exposure. However, other agents are known to produce angiosarcoma of the liver, such as arsenic and Thorotrast® (Gedigke et al. 1975; Marsteller et al. 1975). Enzyme-linked immunoassay (EIA) has been used to detect anti-p53 antibodies in the serum of some individuals with angiosarcoma of the liver before clinical diagnosis of this lesion was made (Trivers et al. 1995). However, not all individuals who develop angiosarcoma of the liver test positive for anti-p53 antibodies; in addition, anti-p53 bodies are not specific only to angiosarcoma of the liver. Further investigation into the ability of this assay to predict individuals at increased risk for developing angiosarcoma of the liver would be useful. Measurement of chromosomal aberrations may indicate the genotoxic effects of vinyl chloride (Anderson et al. 1980; Ducatman et al. 1975; Fucic et al. 1990). However, these aberrations do not specifically indicate vinyl chloride-induced damage. Also, DNA adducts may signal the potential to develop genotoxic effects. Further work identifying the correlation between specific adducts and genotoxic effects would be useful. The cyanosis and blanching of the fingers in response to exposure to the cold may be an early indicator for the development of vinyl chloride disease. However, other conditions also known to produce these symptoms include connective tissue disorders, mechanical arterial obstruction, hyperviscosity of the blood, and exposure to drugs, chemicals, or vibrating tools (Black et al. 1983, 1986; Freudiger et al. 1988). The presence of basophilic stippled

erythrocytes has been reported after inhalation exposure of mice to vinyl chloride (Kudo et al. 1990). Further study would be necessary to determine whether this parameter could be used as a biomarker of effect in humans.

Absorption, Distribution, Metabolism, and Excretion. There are few data on humans for all toxicokinetic parameters across all exposure routes (Krajewski et al. 1980; Sabadie et al. 1980). There are a number of animal studies describing the absorption, distribution, metabolism, and excretion of vinyl chloride administered via the oral route (Feron et al. 1981; Green and Hathway 1978; Watanabe and Gehring 1976; Watanabe et al. 1987a, 1987b; Withey 1976) and the inhalation route (Bolt et al. 1976a, 1977; Buchter et al. 1977, 1980; Filser and Bolt 1979; Guengerich and Watanabe 1979; Hefner et al. 1975b; Jedrychowski et al. 1984, 1985; Ungvary et al. 1978; Watanabe and Gehring 1976; Watanabe et al. 1978a, 1978b; Withey 1976) but few describing the toxicokinetics of vinyl chloride administered via the dermal route. One study in monkeys found an extremely limited absorption of vinyl chloride across the skin (Hefner et al. 1975a). However, only two animals were used, and this was the only study located that examined toxicokinetics after dermal exposure. No information is available regarding dermal absorption of vinyl chloride from liquid or solid media (i.e., water, soil). Dermal exposure from these media is expected to be minimal; however, a study confirming this assumption would be useful. Furthermore, the intermediary metabolites of vinyl chloride appear to be responsible for many of the toxic effects observed. Therefore, information regarding differences in the metabolic pattern according to gender, age, nutritional status, and species and correlations to differences in health effects would also be useful.

Comparative Toxicokinetics. The absorption, distribution, metabolism, and excretion of vinyl chloride have been studied in animals (Bolt et al. 1976a, 1977; Buchter et al. 1977, 1980; Feron et al. 1981; Filser and Bolt 1979; Green and Hathway 1975; Guengerich and Watanabe 1979; Hefner et al. 1975b; Jedrychowski et al. 1984, 1985; Ungvary et al. 1978; Watanabe and Gehring 1976; Watanabe et al. 1976a, 1976b, 1978a, 1978b; Withey 1976), but information on toxicokinetics in humans is extremely limited (Krajewski et al. 1980; Sabadie et al. 1980). Human and animal data indicate that similar target organs (liver, central nervous system) for the toxic effects of vinyl chloride exist, suggesting some similarities of kinetics. Limited information is available regarding interspecies differences in kinetics. Most toxicokinetic studies have been conducted using rats (Bolt et al. 1976a, 1977; Buchter et al. 1977; Feron et al. 1981; Filser and Bolt 1979; Green and Hathway 1975; Guengerich and Watanabe 1979; Hefner et al. 1975b; Jedrychowski et al. 1984, 1985; Ungvary et al. 1978; Watanabe and Gehring 1976; Watanabe et al. 1976a, 1976b, 1978a, 1978b; Withey 1976), but one study in primates indicates that

metabolism may saturate at lower concentrations in primates than rats (Buchter et al. 1980). This may suggest a lower saturation point in humans also. Modeling studies might continue to provide information on the toxicokinetics of vinyl chloride in humans.

Methods for Reducing Toxic Effects. Vinyl chloride appears to be rapidly and completely absorbed following inhalation and oral exposure (Bolt et al. 1977; Krajewski et al. 1980; Watanabe et al. 1976a; Withey 1976). Methods used to reduce absorption immediately after exposure include removal from the source of exposure, cleansing contaminated body parts, and in cases of ingestion, speeding the removal of unabsorbed material from the gastrointestinal tract (Bronstein and Currance 1988; Haddad and Winchester 1990; Stutz and Ulin 1992). No information was located regarding the mechanism of absorption. Additional experiments examining the mechanism of absorption and potential means of interfering with that mechanism would be useful. Distribution of vinyl chloride in the body is rapid and widespread, but storage is limited by rapid metabolism and excretion (Bolt et al. 1976a; Buchter et al. 1977; Watanabe et al. 1976a, 1976b, 1978a). The toxicity of vinyl chloride has been attributed to the formation of reactive epoxide metabolites. No information was located regarding removal of these toxic metabolites from the body once they have been formed, but information from toxicokinetic studies suggest that vinyl chloride metabolism to toxic metabolites may be reduced. Saturation of the metabolic pathways for vinyl chloride can result in the clearance of unmetabolized vinyl chloride in exhaled air (Green and Hathway 1975; Watanabe and Gehring 1976; Watanabe et al. 1976a, 1976b, 1978a). Studies examining the effectiveness and endogenous toxicity of the agents used to block the metabolic pathways (cobaltous chloride, SKF-535-A, 6-nitro-1,2,3-benzothiadiazole) would provide useful information. Another strategy for reducing the formation of toxic metabolites includes increasing the pool of glutathione for use in metabolism to nontoxic metabolites. Studies examining the effectiveness of this procedure would also be helpful. Vinyl chloride disease may be mediated by an autoimmune mechanism (Grainger et al. 1980; Ward 1976). Further studies continuing to examine the role of autoimmune responses in vinyl chloride disease, the genetic factors resulting in greater susceptibility to the disease, and the effectiveness of drugs that block immune responses in reducing the symptoms of vinyl chloride disease would also provide valuable information.

Children's Susceptibility. No studies were located that specifically address the effects of vinyl chloride in children. Some epidemiologic studies (Infante 1976; Infante et al. 1976a, 1976b; NIOSH 1977) have suggested an association between birth defects and vinyl chloride exposure of the parents of affected children. However, the design and analysis of these studies has been criticized (Hatch et al. 1981; Stallones 1987). Some inhalation studies with animals have suggested that vinyl chloride is a

developmental toxicant (i.e., produces delayed ossification), but only at doses that produce significant maternal toxicity (John et al. 1977, 1981; Mirkova et al. 1978; Sal'nikova and Kotsovskaya 1980; Ungvary et al. 1978). No adverse effects on embryo-fetal development were noted in a recent inhalation study in rats conducted using similar concentrations of vinyl chloride (Thornton et al. 2002). There is no evidence that vinyl chloride has hormone-like effects. However, a developmental neurotoxicity study in rats in which pups are tested at various ages after being exposed *in utero* would be informative.

Carcinogenicity studies with animals suggest that younger animals may be more sensitive to the toxicity and carcinogenicity of vinyl chloride (Laib et al. 1985; Maltoni et al. 1981). An age-related sensitivity to DNA adduct formation was noted in rats (Ciroussel et al. 1990; Fedtke et al. 1990; Morinello et al. 2002a). Further mechanistic research may be useful in establishing the mechanism of early life stage sensitivity in laboratory animals and determining whether it is anticipated to be relevant to humans.

No studies were located that specifically address the toxicokinetics of vinyl chloride in children; however, the toxicokinetic behavior of vinyl chloride in children is expected to be similar to that in adults. Young children appear capable of metabolizing vinyl chloride to reactive intermediates that form DNA adducts that lead to cancer. The data on CYP2E1 levels in the developing organism suggest that early life stage sensitivity to vinyl chloride-induced cancer is not solely due to an increase in the production of reactive intermediates via this isozyme. Fetal CYP isoforms may play a role in metabolism of vinyl chloride to reactive intermediates in the fetus and neonate. Glutathione conjugation may also differ in the developing organism. DNA repair capacity and other pharmacodynamic factors may also be associated with an early life stage susceptibility to cancer. Further information on the toxicokinetics and toxicodynamics of vinyl chloride and metabolites during pregnancy, lactation, and early childhood would be useful. The biomarkers of exposure and effects used in occupational worker populations should be evaluated for their relevance to human exposure at all age levels following acute or chronic exposure to vinyl chloride. There are no data on the interaction of vinyl chloride with other chemicals in children. The information available indicates that methods to reduce peak absorption of vinyl chloride are applicable to children.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

The following ongoing studies concerning the adverse health effects associated with vinyl chloride have been identified in the Federal Research in Progress (FEDRIP 2004) database.

Dr. P.W. Brandt-Rauf at Columbia University proposes to investigate whether genetic polymorphisms in vinyl chloride-metabolizing enzymes are also related to the more specific biomarkers of mutagenic damage (mutant *ras*-p21 and/or mutant p53) in vinyl chloride-exposed workers. Restriction fragment length polymorphism techniques will be used to analyze DNA from sub-groups of vinyl chloride-exposed workers. It is anticipated that workers with genetic polymorphisms will be more likely to have the biomarkers of mutagenic damage than similarly exposed workers without the polymorphisms and thus will be more likely to suffer from the subsequent carcinogenic and other health effects of vinyl chloride exposure. If this proves to be correct, then such special populations at risk could be targeted for more stringent interventions to help prevent the occurrence of vinyl chloride-related occupational diseases. This research is sponsored by the National Institute for Occupational Safety and Health.

Dr. W.K. Kaufman at the University of North Carolina at Chapel Hill will investigate the role of DNA repair in the formation of hprt mutations in vinyl chloride-exposed workers. A subfraction of people exposed to vinyl chloride in the workplace expressed high frequencies of hprt mutations in blood lymphocytes. The possible existence of a DNA repair defect in sensitive workers will be evaluated by studying chlorethylene oxide-induced genotoxicity in lymphoblastoid lines derived from sensitive and resistant people. This project will employ a functional assay for DNA repair capacity in peripheral lymphocytes that measures rejoining of radiation-induced chromatid breaks. This research is supported by the National Institute of Environmental Health Sciences (NIEHS).

Dr. G.E. Kisby at the Oregon Health Sciences University proposes experiments to examine the relationship between the formation of etheno base DNA adducts of chloroacetaldehyde and neurotoxicity or mutations. Neuronal and astrocyte cell cultures will be developed from different brain regions (e.g., cortex, hippocampus, midbrain, cerebellum) of DNA repair proficient and deficient mice (i.e., k N-methylpurine DNA glycosylase Aag). These cell lines will be examined for acute and delayed chloroacetaldehyde-induced neurotoxicity. Separate sets of astrocyte cell cultures will be developed from hprt heterozygous-deficient mice and examined to determine the spectrum of chloroacetaldehyde-induced

mutations. Findings from these studies are expected to provide important information about the neurotoxic and mutagenic mechanisms of vinyl chloride. This research is sponsored by the NIEHS.

4. CHEMICAL AND PHYSICAL INFORMATION

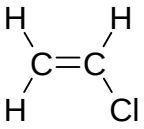
4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of vinyl chloride is located in Table 4-1. This information includes synonyms, chemical formula and structure, and identification numbers.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of vinyl chloride is located in Table 4-2.

Table 4-1. Chemical Identity of Vinyl Chloride

Characteristic	Information	Reference
Chemical name	Vinyl chloride	HSDB 2004
Synonym(s)	Chloroethene; chloroethylene; 1-chloroethylene; ethylene monochloride; monovinyl chloride; monochloroethene; monochloroethylene; MVCs; Trovidur; VC; VCM; vinyl chloride monomer	Fire 1986; HSDB 2004
Registered trade name(s)	No data	
Chemical formula	C_2H_3Cl	HSDB 2004
Chemical structure		HSDB 2004
Identification numbers:		
CAS registry	75-01-4	HSDB 2004
NIOSH/RTECS	KU9625000	HSDB 2004
EPA hazardous waste	U043	HSDB 2004
OHM/TADS	7216947	HSDB 2004
DOT/UN/NA/IMCO shipping	1086	HSDB 2004
HSDB	169	HSDB 2004
NCI	No data	HSDB 2004

CAS = Chemical Abstract Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Vinyl Chloride

Property	Information	Reference
Molecular weight	62.5	Lewis 1996
Color	Colorless	Budavari 1989
Physical state	Gas	Budavari 1989
Melting point	-153.8 °C	Budavari 1989
Boiling point	-13.37 °C	Budavari 1989
Density:		
at -14.2 °C	0.969 g/cm^3	Cowfer and Magistro 1983
at 15 °C	0.9195 g/cm^3	Lewis 1996
at 20 °C	0.9106 g/cm^3	NIOSH 1986
Vapor density	2.16	Fire 1986
Odor	Sweet	HSDB 1996
Odor threshold:		
Water	3.4 ppm	Amoore and Hautala 1983
Air	3,000 ppm	Amoore and Hautala 1983
Solubility:		
Water at 25 °C	2,763 mg/L	EPA 1985b
	1,100 mg/L	Cowfer and Magistro 1983
Organic solvent(s)	Soluble in hydrocarbons, oil, alcohol, chlorinated solvents, and most common organic liquids	Cowfer and Magistro 1983
Partition coefficients:		
Log K_{ow}	1.36	NIOSH 1986
Log K_{oc}	1.99	Lyman et al. 1982
Vapor pressure:		
at 20 °C	2,530 mmHg	Budavari 1989
at 25 °C	2,600 mmHg	Lewis 1996
Henry's law constant:		
10.3 °C	0.0147 (atm-m^3)/mol	Gossett 1987
17.5 °C	0.0193 (atm-m^3)/mol	Gossett 1987
24.8 °C	0.0278 (atm-m^3)/mol	Gossett 1987
34.6 °C	0.0358 (atm-m^3)/mol	Gossett 1987
Autoignition temperature	472 °C	Lewis 1996
Flashpoint	-78 °C (closed cup)	Budavari 1989
Flammability limits	3.6–33 volume %	NIOSH 1986
Conversion factors:		
ppm to mg/m^3 in air	1 ppm=2.6 mg/m^3	NIOSH 1990
mg/m^3 to ppm in air	1 mg/m^3=0.38 ppm	NIOSH 1990
Explosive limits	4–22 volume %	Lewis 1996

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Vinyl chloride was first produced commercially in the 1930s by reacting hydrogen chloride with acetylene. Currently, vinyl chloride is produced commercially by the chlorination of ethylene through one of two processes, direct chlorination or oxychlorination. Direct chlorination reacts ethylene with chlorine to produce 1,2-dichloroethane. Similarly, oxychlorination produces 1,2-dichloroethane, but this is accomplished by reacting ethylene with dry hydrogen chloride and oxygen. After both processes, the 1,2-dichloroethane is subjected to high pressures (2.5–3.0 megapascals) and temperatures (550–550 °C). This causes the 1,2-dichloroethane to undergo pyrolysis, or thermal cracking, which forms the vinyl chloride monomer and hydrogen chloride. The vinyl chloride monomer is then isolated (Cowfer and Magistro 1985). The technical-grade product is available in 99.9% purity (HSDB 2004). Efforts are being made to minimize by-product formation (hydrocarbons, chlorinated hydrocarbons, and unreacted material) in 1,2-dichloroethane pyrolysis (Cowfer and Magistro 1985).

Table 5-1 summarizes the facilities in the United States that either manufacture or process vinyl chloride. This information was obtained from the Toxic Release Inventory (TRI02 2004), and also lists the maximum amounts of vinyl chloride that are present at these sites and the end uses of vinyl chloride. Table 5-2 lists the facilities that solely manufacture vinyl chloride for commercial purposes and their production capacities. In 2001, the global demand for vinyl chloride was 14.89 billion pounds; in 2002, demand was 15.94 billion pounds; and in 2006, it is estimated that demand for vinyl chloride will be 17.8 billion pounds (CMR 2003). Demand for vinyl chloride monomer is almost entirely dependent upon the consumption of polyvinyl chloride (PVC) materials. Demand is expected to increase globally at a rate of approximately 3.5% annually due to increasing demand in Asia, while demand in the United States is expected to increase by about 2.8% annually (CMR 2003).

5.2 IMPORT/EXPORT

Imports of vinyl chloride totaled 29 million pounds (13.17 million kilograms) in 1994 and 164 million pounds in 1991 (CPS 1993; NTD 1995). Imports have been steadily declining from a high of 302 million pounds in 1989, prior to which they had been increasing (CPS 1993). Currently, the amounts of vinyl

Table 5-1. Facilities that Produce, Process, or Use Vinyl Chloride

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	1	100,000	999,999	6
AR	2	10,000	999,999	6, 12
CA	1	1,000,000	9,999,999	2, 3, 6
DE	2	1,000,000	9,999,999	2, 3, 6
IL	2	1,000,000	49,999,999	6
KS	1	1,000	9,999	2, 3, 6, 10
KY	6	10,000	49,999,999	2, 3, 4, 6, 12, 14
LA	12	1,000	99,999,999	3, 4, 5, 6, 12, 13
MI	2	10,000	999,999	2, 3, 6, 12
MO	1	100,000	999,999	5, 6
MS	1	10,000,000	49,999,999	6
NC	1	0	99	5
NJ	3	1,000,000	49,999,999	6
OH	3	1,000	9,999	12
OK	1	1,000,000	9,999,999	6
PA	1	1,000,000	9,999,999	6
TX	12	0	499,999,999	2, 3, 4, 5, 6, 9, 12, 14
UT	1	1,000	9,999	12

Source: TRI02 2004 (Data are from 2002)

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Table 5-2. U.S. Production Capacity of Vinyl Chloride[a]

U.S. Producer	Location	Capacity (millions pounds per year)
Dow Chemicals	Oyster Creek, Texas; Freeport, Texas	2,700
Dow Chemicals	Plaquemine, Louisiana	1,500
Formosa Plastics	Baton Rouge, Louisiana	980
Formosa Plastics	Point Comfort, Texas	1,235
Geismar Vinyls	Geismar, Louisiana	650
Georgia Gulf	Lake Charles, Louisiana	1,000
Georgia Gulf	Plaquemine, Louisiana	1,600
Oxy Mar	Ingleside, Texas	2,300
Oxy Vinyls	Deer Park, Texas	1,300
Oxy Vinyls	La Porte, Texas	2,400
PHH Monomers	Lake Charles, Louisiana	1,300
Westlake Monomers	Calvert City, Kentucky	1,200
U.S. total capacity: 18,165 million pounds		

[a]CMR 2003

chloride imported into the United States are negligible (CMR 2003). Exports of vinyl chloride were 1.65 billion pounds (0.75 billion kilograms) in 1992 and 2.10 billion pounds (0.95 billion kilograms) in 1994 (NTD 1995). Recent estimates have shown a slight decrease in U.S. export volumes. In 2001, exports of vinyl chloride totaled 1.89 billion pounds and in 2002, exports were 1.43 billion pounds (CMR 2003).

5.3 USE

Vinyl chloride is an important industrial chemical because of its wide variety of end-use products and the low cost of producing polymers from it. Approximately 98% of all vinyl chloride produced is used to manufacture PVC materials (CMR 2003). These PVC materials are widely used in automotive parts, packaging products, pipes, construction materials, furniture, and a variety of other products (Cowfer and Magistro 1985). Other miscellaneous uses, which account for about 2% of the vinyl chloride that is produced annually, include the production of 1,1,1-trichloroethane and copolymers with vinyl acetate, vinyl sterate, and vinylidene chloride (CMR 2003).

Vinyl chloride has been used in the past as a refrigerant, as an extraction solvent for heat-sensitive materials, and in the production of chloroacetaldehyde and methyl chloroform (IARC 1979). In the United States, limited quantities of vinyl chloride were used as an aerosol propellant and as an ingredient of drug and cosmetic products; however, these practices were banned by the EPA in 1974 (HSDB 2004; IARC 1979).

5.4 DISPOSAL

Since vinyl chloride has been identified by EPA as a hazardous material, its disposal is regulated under the Federal Resource Conservation and Recovery Act (RCRA) (EPA 1993d). The transportation of hazardous materials for disposal is regulated by the Department of Transportation in compliance with this act (DOT 1993). The recommended method of disposal is total destruction by incineration. The temperature of the incinerator must be sufficient to ensure the complete combustion of the vinyl chloride in order to prevent the formation of phosgene. The recommended temperature range for incineration is 450–1,600 °C, with residence times of seconds for gases and liquids, and hours for solids (HSDB 2004). If in solution, the vinyl chloride product may need to be adsorbed onto a combustible material prior to incineration. Recommended materials include vermiculite, sawdust, or a sand-soda ash mixture (90/10)

covered with wood and paper (OHM/TADS 1985). The vinyl chloride can also be dissolved in a flammable solvent prior to incineration. An acid scrubber should be used in conjunction with the incinerator in order to remove any hydrogen chloride that is produced by the combustion process (HSDB 2004; OHM/TADS 1985). Alternatively, chemical destruction may be used, especially with small quantities. From 1 to 2 days is generally sufficient for complete destruction (HSDB 2004).

Aqueous byproduct solutions from the production of vinyl chloride are usually steam-stripped to remove volatile organic compounds, neutralized, and then treated in an activated sludge system to remove nonvolatile organic compounds remaining in the waste water (Cowfer and Magistro 1983).

6. POTENTIAL FOR HUMAN EXPOSURE

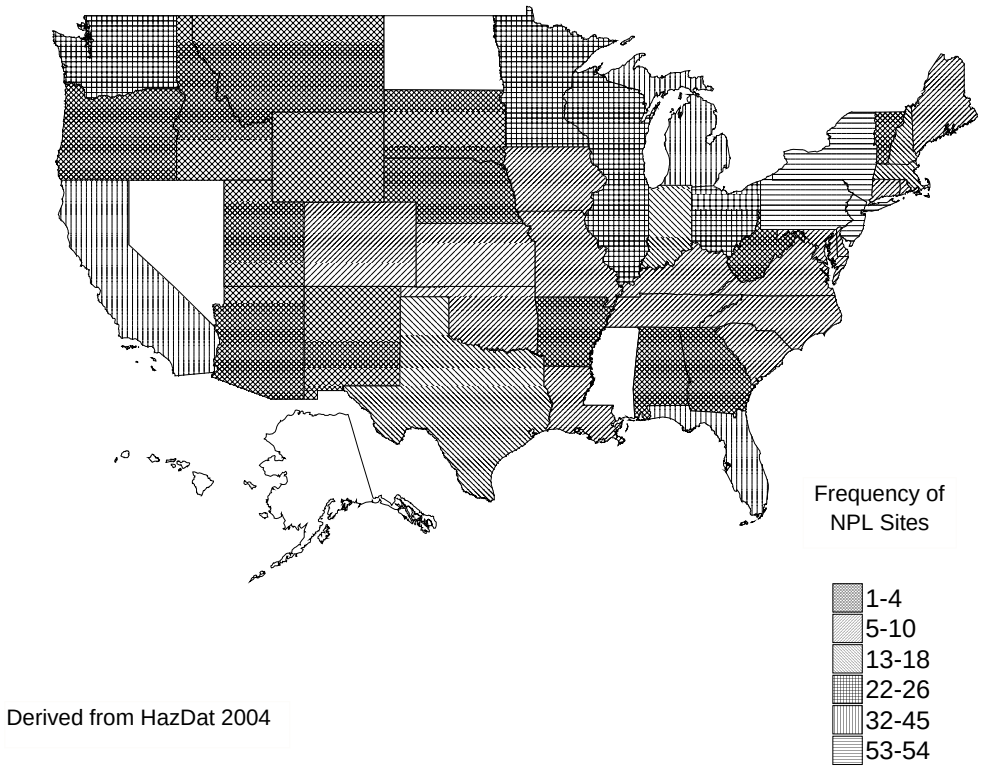
6.1 OVERVIEW

Vinyl chloride has been identified in at least 616 of the 1,647 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2004). However, the number of sites evaluated for vinyl chloride is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, all are located within the continental United States with the exception of one site located in the Virgin Islands and one site in the Commonwealth of Puerto Rico (not shown).

Vinyl chloride is used almost exclusively in the United States by the plastics industry for the production of polyvinyl chloride (PVC) and several copolymers. Anthropogenic sources are responsible for all of the vinyl chloride found in the environment. Most of the vinyl chloride released to the environment eventually escapes to the atmosphere. Lesser amounts are released to groundwater. Vinyl chloride has been detected in the ambient air in the vicinity of vinyl chloride and PVC manufacturing plants and hazardous waste sites. The compound has also leached into groundwater from spills, landfills, and industrial sources; it can also enter groundwater after being produced by the bacterial degradation of trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane (Smith and Dragun 1984).

Effluents and emissions from vinyl chloride and PVC manufacturers are responsible for most of the vinyl chloride released to the environment. When released to the atmosphere, vinyl chloride is expected to be removed by reaction with photochemically generated hydroxyl radicals (half-life=1–2 days). Reaction products include hydrochloric acid, formaldehyde, formyl chloride, acetylene, chloroacetaldehyde, chloroacetylchloranil, and chloroethylene epoxide. In photochemical smog, the half-life of vinyl chloride is reduced to a few hours. When released to water, volatilization is expected to be the primary environmental fate process. In waters containing photosensitizers, such as humic materials, sensitized photodegradation may also be important. Sensitized photodegradation may occur when a molecule other than the compound of interest absorbs light, promoting it to an excited state; a transfer of energy occurs between the excited state of the photosensitizer and the compound of interest, which involves no direct absorption of photons by that particular compound. When released to soil, vinyl chloride either volatilizes rapidly from soil surfaces or leaches readily through soil, ultimately entering groundwater.

Figure 6-1. Frequency of NPL Sites with Vinyl Chloride Contamination



Segments of the general population living in the vicinity of emission sources are exposed to vinyl chloride by inhalation of contaminated air. Average daily intake of vinyl chloride by inhalation for these people ranges from trace amounts to 2,100 µg/day. The average daily intake of vinyl chloride by inhalation is expected to be very low for the remainder of the population. The majority of the general population is not expected to be exposed to vinyl chloride through ingestion of drinking water. The average daily intake of vinyl chloride through the diet is essentially zero. Workers, particularly in plastic industries, are exposed to vinyl chloride mainly by inhalation, with some absorption through the skin possible. The National Occupational Exposure Survey (NOES), conducted by NIOSH from 1981 to 1983, estimated that 81,314 workers employed at 3,711 plant sites were potentially exposed to vinyl chloride (NOES 1990).

6.2 RELEASES TO THE ENVIRONMENT

6.2.1 Air

The major source of vinyl chloride releases to the environment is believed to be emissions and effluents from plastic industries, primarily vinyl chloride and PVC manufacturers. Worldwide emissions of vinyl chloride into the atmosphere during 1982 totaled approximately 400 million pounds (Hartmans et al. 1985). Another emission source is tobacco smoke, which has been found to contain 5.6–28 ng vinyl chloride per cigarette (Hoffman et al. 1976). According to TRI data for 2002 (TRI02 2004), an estimated total of 670,992 pounds of vinyl chloride, amounting to 83% of the total environmental releases, was discharged to the air from the manufacturing and processing facilities in the United States in 2001 (Table 6-1). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list. Vinyl chloride was detected in the air at 63 of the 1,647 current or former EPA NPL hazardous waste sites (HazDat 2004).

6.2.2 Water

Vinyl chloride released in waste water from the plastics industries is expected to volatilize fairly rapidly (on the order of hours to days) into the atmosphere. Anaerobic reductive dehalogenation of trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane also releases vinyl chloride into groundwater at hazardous waste sites (Smith and Dragun 1984) or other locations where the proper conditions are found in the subterranean strata. Vinyl chloride leaches into groundwater from spills,

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Vinyl Chloride[a]

		Reported amounts released in pounds per year[b]						
						Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	On-site[i]	Off-site[j]	On- and off-site
AL	1	2,823	No data	0	0	2,823	0	2,823
AR	2	6,587	No data	0	0	6,587	0	6,587
CA	1	9,539	0	0	0	9,539	0	9,539
DE	2	139,656	1	0	5	139,657	5	139,662
IL	2	64,382	14	0	6	64,396	6	64,402
KS	1	13	No data	12	0	25	0	25
KY	6	49,507	4	0	1	49,511	1	49,512
LA	12	77,481	192	139,450	42	217,123	42	217,165
MI	2	535	0	0	0	535	0	535
MO	1	91	0	0	0	91	0	91
MS	1	28,069	No data	0	0	28,069	0	28,069
NC	1	16	No data	0	0	16	0	16
NJ	3	30,520	39	0	39	30,559	39	30,598
OH	3	255	5	0	255	260	255	515
OK	1	2,500	0	0	0	2,500	0	2,500
PA	1	97,100	0	0	0	97,100	0	97,100
TX	12	161,918	288	0	1	162,206	1	162,207
Total	52	670,992	543	139,462	349	810,997	349	811,346

Source: TRI02 2004 (Data are from 2002)

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[j]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

landfills, and industrial sources (TRI02 2004). According to data collected from the analysis of leachates and monitoring wells at sites where groundwater was contaminated by municipal solid waste landfill leachate, vinyl chloride was present in both the leachates and the groundwater samples (Sabel and Clark 1984). Vinyl chloride has been found in groundwater at other landfills also (Agency for Toxic Substances and Disease Registry 1995a, 1995b). Vinyl chloride was detected in groundwater at 325 of the 1,647 current or former EPA NPL hazardous waste sites, and in surface water at 109 of the 1,647 current or former EPA NPL hazardous waste sites (HazDat 2004).

According to TRI data for 2002 (TRI02 2004), an estimated total of 543 pounds of vinyl chloride, constituting <1% of the total environmental releases, was discharged to the water from the manufacturing and processing facilities in the United States (Table 6-1). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

6.2.3 Soil

Vinyl chloride can either enter the soil from leachates at hazardous waste sites or enter the ground via underground injection. Release through either of these mechanisms is, however, only a small fraction of the total environmental discharge (TRI02 2004). According to TRI data for 2002 (TRI02 2004), an estimated total of 349 pounds of vinyl chloride, amounting to <1% of the total environmental releases, was discharged to the soil from manufacturing and processing facilities in the United States in 2002 (Table 6-1). The TRI also reported that 139,462 pounds of vinyl chloride, amounting to about 17% of the total released was injected underground (TRI02 2004). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list. Vinyl chloride was detected in soil at 158 of the 1,647 current or former EPA NPL hazardous waste sites, and in sediment at 47 of the 1,647 current or former EPA NPL hazardous waste sites (HazDat 2004).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Based on a vapor pressure of 2,660 mmHg at 25 °C, essentially all vinyl chloride in the atmosphere is expected to exist solely as a gas (Eisenreich et al. 1981; Verschueren 1983). Consequently, removal from the atmosphere by dry deposition is not expected to be an important fate process.

The primary transport process for vinyl chloride from natural water systems is volatilization into the atmosphere. The Henry's law constant of vinyl chloride has been measured as 0.0278 atm-m^3/mol at 24.8 °C (Gossett 1987), which suggests that vinyl chloride should partition rapidly to the atmosphere. The half-life for vinyl chloride volatilization from a typical pond, river, and lake has been estimated to be 43.3, 8.7, and 34.7 hours, respectively. These values are based on an experimentally determined reaeration rate ratio of approximately 2 and assumed oxygen reaeration rates of 0.008, 0.04, and 0.01 per hour for a typical pond, river, and lake, respectively (EPA 1982a). Predicted half-lives should be considered rough estimates since the presence of various salts in natural water systems may affect the volatility of vinyl chloride significantly (EPA 1979d). Many salts have the ability to form complexes with vinyl chloride and can increase its water solubility; therefore, the presence of salts in natural waters may significantly influence the amount of vinyl chloride remaining in the water (EPA 1979d). The half-life of vinyl chloride in bodies of water is also affected by depth and turbidity.

The relatively high vapor pressure of vinyl chloride indicates that the compound volatilizes quite rapidly from dry soil surfaces (Verschueren 1983). The effective half-life (due to volatilization and degradation) of vinyl chloride incorporated 10 cm deep in dry soil is predicted to be 12 hours (Jury et al. 1984). Vinyl chloride is soluble in water and thus can leach through the soil and enter groundwater before evaporation can occur (Cowfer and Magistro 1983).

Experimental data regarding adsorption of vinyl chloride to soil were not located. Based on the regression equations given by Lyman et al. (1982), Sabljic (1984), and Kenaga and Goring (1980), the soil organic carbon adsorption coefficient (K_{oc}) for vinyl chloride was estimated to range from 14 to 131. These K_{oc} values suggest a very low sorption tendency, meaning that this compound would be highly mobile in soil. Thus, vinyl chloride has the potential to leach into groundwater.

Vinyl chloride is soluble in most common organic solvents (Cowfer and Magistro 1983). In situations where organic solvents exist in relatively high concentrations (e.g., landfills, hazardous waste sites), cosolvation of vinyl chloride could have the effect of reducing its volatility, thus causing it to have even greater mobility than indicated by estimated K_{oc} values.

Vinyl chloride's small octanol/water partition coefficient (log K_{ow}=1.23) indicates that the potential for bioconcentration in aquatic organisms is low (EPA 1982a). Using a log K_{ow} of 1.23 and a regression derived equation (Meylan et al. 1999), the bioconcentration factor (BCF) for vinyl chloride is estimated as 3. Freitag et al. (1985) measured BCFs in algae, fish, and activated sludge. The BCFs for algae, fish,

and activated sludge were 40, <10, and 1,100, respectively. The very low value for fish, in comparison to the algae and activated sludge, may suggest a detoxification process in more highly developed organisms such as fish. Lu et al. (1977) examined the bioaccumulation of ^{14}C-vinyl chloride in a closed model aquatic ecosystem over a 3-day period. The high volatility of vinyl chloride minimized any potential bioaccumulation. Relatively low tissue concentrations found in fish suggested that vinyl chloride is not biomagnified in aquatic food chains to any substantial degree.

6.3.2 Transformation and Degradation

6.3.2.1 Air

Reaction of gaseous vinyl chloride with photochemically generated hydroxyl radicals is predicted to be the primary degradation mechanism for this compound in the atmosphere (Cox et al. 1974; Howard 1976; Perry et al. 1977). The rate constant for this reaction has been measured as 6.96×10^{-12} cm^3/molec-second (Kwok and Atkinson 1994). This rate constant corresponds to an atmospheric half-life of about 18 hours assuming a hydroxyl radical concentration of 1.5×10^6 molecules/cm^3. Products of this reaction are hydrochloric acid, formaldehyde, formyl chloride, carbon monoxide, carbon dioxide, chloroacetaldehyde, acetylene, chloroethylene epoxide, chloroacetylchloranil, and water (Müller and Korte 1977; Woldbaek and Klaboe 1978). Under conditions of photochemical smog, the half-life of vinyl chloride would be reduced to a few hours (Carassiti et al. 1977). Reaction with ozone, nitrate radicals and direct photolysis are less important degradation mechanisms of vinyl chloride in the atmosphere (EPA 1976a, 1985c; Zhang et al. 1983). Vinyl chloride in the gas phase does not absorb light of wavelengths above 220 nm (EPA 1976a). Since atmospheric ozone blocks almost all sunlight with wavelengths <295 nm, direct photolysis is likely to occur very slowly, if at all, in the atmosphere (EPA 1976a).

6.3.2.2 Water

The primary removal process for vinyl chloride from surface waters is volatilization into the atmosphere. Vinyl chloride in water does not absorb ultraviolet radiation above 218 nm; therefore, direct photolysis in the aquatic environment is expected to occur very slowly, if at all (EPA 1976a). In sunlit surface waters containing photosensitizers, such as humic materials, photodegradation may be more rapid. If so, in some waters, sensitized photodegradation may be an important removal mechanism (EPA 1976a).

The hydrolytic half-life of vinyl chloride has been estimated to be <10 years at 25 °C (EPA 1976a). Since the volatilization rate of vinyl chloride is much more rapid than the predicted rate of hydrolysis, hydrolysis is not a significant aquatic fate (EPA 1976a, 1979d). Vinyl chloride is not oxidized chemically by reaction with photochemically generated molecular oxygen in natural water systems (EPA 1976a). Experiments carried out at 20 mg/L vinyl chloride in water saturated with molecular oxygen at elevated temperatures showed that, after 12 hours at 85 °C, no degradation of vinyl chloride was observed. At temperatures and oxygen concentrations in natural waters, therefore, vinyl chloride is not expected to degrade by molecular oxygen at a significant rate (EPA 1976a).

EPA (1977) observed no change in the biochemical oxygen demand in raw sewage seed (used as a microbial inoculum) and raw sewage seed plus vinyl chloride at 20 °C over a 25-day period. The study authors interpreted this to mean that no biodegradation of vinyl chloride occurred. However, more recent data has shown that vinyl chloride can undergo microbial degradation under aerobic conditions. *Rhodococcus* sp. strains SM-1 and Wrink, which were isolated from a trichloroethylene-degrading bacterial mixture, and *Rhodococcus rhodochrous* ATCC 21197 were shown to degrade >99.9% of vinyl chloride within 7 days (Malachowsky et al. 1994). No significant differences in the amount of vinyl chloride degraded were found among the three organisms. The majority (66–83%) of the labeled carbon was metabolized to carbon dioxide (CO_2).

Vinyl chloride (1 ppm) was rapidly degraded under aerobic conditions in a laboratory study that used soil-water microcosms from aquifer material without the addition of other nutrients, such as nitrogen and phosphorus (Davis and Carpenter 1990). About 25% of the vinyl chloride was degraded after 1 week and more than 99% was degraded after 108 days. Sixty-five percent of labeled vinyl chloride was recovered as $^{14}CO_2$ after 108 days, demonstrating the extent of the mineralization.

Rhodococcus sp. Strain SM-1, a member of the order *Actinomycetales*, obtained from a trichloroethylene-degrading consortium was found to mineralize vinyl chloride to CO_2 by using propane as an energy source during growth experiments or cell suspension experiments (Phelps et al. 1991). Vinyl chloride concentrations decreased by more than 90%; growth cultures and cell suspensions incorporated about 10% of the transformed vinyl chloride into biomass (Phelps et al. 1991). *Mycobacterium vaccae* JOB5 degraded 100% of vinyl chloride in a 2-hour incubation (Wackett et al. 1989).

Degradation of vinyl chloride generally occurs slowly in anaerobic groundwater and sediment; however, under methanogenic or Fe(III) reducing conditions anaerobic degradation occurs more rapidly. Vinyl

chloride was mineralized approximately 34% in 84 hours in anaerobic aquifer microcosms supplemented with Fe(III) and held under Fe(III) reducing conditions (Bradley and Chapelle 1996).

6.3.2.3 Sediment and Soil

Most vinyl chloride present on soil surfaces will volatilize to the atmosphere. Vinyl chloride is also mobile in soil and susceptible to leaching (Lyman et al. 1982). The presence of other organic solvents, such as those found at hazardous waste sites, may affect the mobility of the substance in the soil (Cowfer and Magistro 1983). Photodegradation on the surface of soils is expected since sensitized photodegradation in water occurs.

Several laboratory studies have indicated that both aerobic and anaerobic biodegradation of vinyl chloride can occur in soils and aquifer materials via a number of mechanisms (Barrio-Lage et al. 1990; Castro et al. 1992a, 1992b; Davis and Carpenter 1990), although these degradation processes were generally slow. More recently, Nelson et al. (1993) investigated methanotrophic degradation of vinyl chloride using a laboratory-scale, methanotrophic, attached-film, expanded-bed bioreactor. They found that this technique is an efficient way to degrade vinyl chloride, with the removal efficiency >90%. Under methanotrophic conditions, vinyl chloride was mineralized between 5 and 44% over 37 days using creek bed sediment microcosms obtained from a naval station near Jacksonville, Florida (Bradley and Chapelle 1997). Slightly higher mineralization rates were observed under Fe(III) reducing conditions.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

Air in rural/remote and urban/suburban areas of the United States typically contains very low or no detectable amounts of vinyl chloride (EPA 1982f; Grimsrud and Rasmussen 1975a, 1975b; Harkov et al. 1984; Pratt et al. 2000; Stephens et al. 1986; Wallace et al. 1984). The mean concentration of vinyl chloride from 3,650 samples monitored in the state of Minnesota over an 8-year study period (1991–1998) was 0.01 µg/m^3, with a maximum observed value of 1.77 µg/m^3 (Pratt et al. 2000). Sampling was performed at 25 different sites across the state with sampling sites chosen to measure concentrations of pollutants near specific point sources, or to collect baseline data near the Minneapolis-St. Paul area.

Limited monitoring data indicate that in areas near vinyl chloride and PVC manufacturing facilities, the concentration of vinyl chloride in air typically ranges from trace levels to 105 μg/m^3 (0.041 ppm) (EPA 1979a, 1982f; Gordon and Meeks 1977) but may exceed 2,600 μg/m^3 (1 ppm) (Fishbein 1979). Elevated levels of vinyl chloride may also be found in the vicinity of hazardous waste sites and municipal landfills. Concentrations ranging from below detection limits to 5–8 μg/m^3 (0.002–0.003 ppm) have been measured in the air above some landfills (Baker and Mackay 1985; Stephens et al. 1986). Homes near one hazardous waste site in southern California were found to contain levels as high as 1,040 μg/m^3 (0.4 ppm) (Stephens et al. 1986) and homes near another site contained between 1 and 9 ppb (Miller and Beizer 1985). Gaseous emissions from 20 Class II (nontoxic) landfills in southern California were analyzed for vinyl chloride (Wood and Porter 1987). Vinyl chloride was found in emissions from 85% of the landfills tested, and concentrations >2,600 μg/m^3 (1 ppm) were detected in more than half of the landfill emissions. The concentrations of vinyl chloride measured in this study ranged from 0.624 to 114.4 mg/m^3 (0.24–44 ppm). Based on their observations, the study authors concluded that the presence of vinyl chloride at these landfills was due to either illegal disposal or *in situ* generation by the degradation of chlorinated solvents by bacteria and other microbes (Wood and Porter 1987). Ambient air monitoring data downwind from the Eastview Road Landfill located in Guelph, Ontario indicated the presence of vinyl chloride at low levels. Concentrations ranging from 0.0023 to 0.042 μg/m^3 were observed downwind from this facility during sampling conducted in May and June 1993 (Chadder 1994).

6.4.2 Water

Vinyl chloride has been detected at varying concentrations in surface water, groundwater, and drinking water throughout the United States. Concentrations of vinyl chloride in drinking water wells and surface water in New York State were found to be 50 μg/L (0.05 ppm) and 10 μg/L (0.01 ppm), respectively (Burmaster 1982). Monitoring studies in nine states have identified concentrations as high as 380 μg/L (0.38 ppm) in groundwater (Dyksen and Hess 1982). Vinyl chloride levels ranged from below the detection limit (0.64 μg/L) to 55.6 μg/L (3.35 μg/L mean value) in river water sampled near vinyl chloride and PVC manufacturing facilities in Osaka, Japan (Yamamoto et al. 2001).

Levels of vinyl chloride in groundwater in the United States were determined during the 1982 EPA Groundwater Supply Survey (Westrick et al. 1984). Water supplies from 945 sites throughout the United States were studied. Vinyl chloride was positively identified in only 0.74% of the 945 groundwater supplies (detection limit 0.001 ppm). It was reported that 0.5% of 186 random sample sites and 3.8% of 158 nonrandom sample sites contained detectable levels of vinyl chloride. The maximum concentrations

at the random and nonrandom sites were 1.1 µg/L (0.0011 ppm) and 8.4 µg/L (0.0084 ppm), respectively (Westrick et al. 1984). Approximately half of the samples were taken from a random list of water systems, which were subdivided into two sets of systems—those serving fewer than 10,000 people and those serving more than 10,000 people. The nonrandom samples were taken from systems selected by the states, using groundwater sources that were likely to include volatile organic compounds in drinking water (Westrick et al. 1984). Other studies have reported the occurrence of vinyl chloride in groundwater samples collected throughout the United States at levels at or below 380 µg/L (0.38 ppm) (Cotruvo 1985; EPA 1982f; Goodenkauf and Atkinson 1986; Stuart 1983). In a study of three landfills located in Orange County, Florida, vinyl chloride was detected in water samples obtained at four out of nine wells with average concentrations ranging from 2.0 to 26.5 µg/L (Hallbourg et al. 1992). In a survey of 30 industrial sites located in Taiwan, vinyl chloride was detected in six groundwater wells at concentrations of 100,000 (1993 sampling period) and 22,000 µg/L (1994 sampling period) (Kuo et al. 2000).

6.4.3 Sediment and Soil

Monitoring data for vinyl chloride in soil were not located in the available literature.

6.4.4 Other Environmental Media

In the past, vinyl chloride had been detected in various foods and bottled drinking water as a result of migration from PVC food wrappings and containers (Benfenati et al. 1991; Gilbert et al. 1980). Vinyl chloride has been found in vinegar at levels up to 98,000 µg/L (98 ppm), in edible oils at 300–1,800 µg/L (0.3–1.8 ppm), and in alcoholic beverages at 0.0–8,400 µg/L (0.0–8.4 ppm) when these foods were packaged and stored in PVC containers (Williams 1976; Williams and Miles 1975). At present, the Food and Drug Administration (FDA) regulates the use of PVC polymers in food packaging materials and the amount of residual monomer in polymers and as a result, significant reduction in the levels of vinyl chloride in food samples has been achieved since the early 1970s (WHO 1999). In 1986, FDA determined that thick-walled PVC food packaging (i.e., bottles and blister packages) was safe provided that the polymer contained <10 ppb vinyl chloride (McNeal et al. 2003). To determine whether the residual vinyl chloride levels in PVC containing food packages in current use are <10 ppb, a survey and analysis of PVC containing food packages was recently conducted (McNeal et al. 2003). The results showed that vinyl chloride levels found in the packages ranged from none detected (<1 ppb) to about 275 ppb. The package containing 275 ppb residual vinyl chloride was a not a food contact material

(McNeal et al. 2003). Dietary exposure to vinyl chloride from PVC packages used for food has been calculated by several agencies, and based upon estimated average intakes in the United Kingdom and the United States, an exposure of <0.0004 µg/kg/day was estimated for the late 1970s and early 1980s (WHO 1999).

In a modeling study using liquid chromatography to simulate migration conditions of vinyl chloride from PVC in actual food packaging and storage, it was shown that at the very low concentrations (<1 ppm) of residual vinyl chloride monomer in PVC packaging material, "essentially zero" migration of the vinyl chloride monomer into foods occurs (Kontominas et al. 1985). Vinyl chloride levels were determined in Italian drinking water bottled in PVC; levels ranged from 13 to 83 parts per trillion (ppt) (mean, 48 ppt) (Benfenati et al. 1991). It was also determined that there was a progressive migration of vinyl chloride from the bottle to the water, which occurred at a rate of 1 ng/L/day (Benfenati et al. 1991). Vinyl chloride was also detected in bottled water from Saudi Arabia packaged in PVC bottles at levels of ≤0.6 ppb (Fayad et al. 1997).

Vinyl chloride has been detected in municipal drinking water supplies. A study by EPA (1982f) estimated that 12 of 11,202 public water supplies that used surface water as their primary source had levels of vinyl chloride between 1.0 µg/L (0.001 ppm) and 5.0 µg/L (0.005 ppm); none had levels above 5 µg/L (0.005 ppm). Another study found that drinking water that ran through PVC pipes contained vinyl chloride at 1.4 µg/L (0.0014 ppm), whereas water that ran through a PVC system 9 years older contained 0.03–0.06 µg/L (0.03–0.06 ppb) (Dressman and McFarren 1978). The amount of vinyl chloride migrating from rigid PVC water pipes into drinking water was directly proportional to the residual level of vinyl chloride in the pipe itself. Current data on levels of vinyl chloride in drinking water and on the potential for leaching of vinyl chloride from PVC pipes were not located. Under certain test conditions, vinyl chloride in drinking water reacts with chlorine and is converted to chloroacetaldehyde and chloroacetic acid (Ando and Sayato 1984). Information concerning the effect of this reaction on drinking water supplies that are treated with chlorine and the extent of this reaction was not stated.

During an EPA study, detectable levels of vinyl chloride were found in indoor air samples taken from two of seven new 1975 model cars. Levels of vinyl chloride in indoor air in the two cars ranged from 400 to 1,200 µg/L (0.4–1.2 ppm). Ventilation of the car interiors led to the dissipation of vinyl chloride. The cars involved in the study had a high ratio of plastic to interior volume and were expected to provide worst-case concentrations for vinyl chloride in interior car air (EPA 1976b). Because of the limited

nature of these data and the fact that this study is somewhat dated, no conclusions can be drawn regarding levels of vinyl chloride monomer in interior air of cars currently being produced.

Vinyl chloride has been detected in tobacco smoke. Cigarette smoke and smoke from small cigars has been found to contain 5.6–27 ng vinyl chloride per cigarette (Hoffman et al. 1976). The study authors suggested that the inorganic chloride concentrations in the tobacco determine the amount of vinyl chloride formed upon combustion of tobacco and released into the smoke (Hoffman et al. 1976).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Inhalation of ambient or workplace air containing vinyl chloride is the most likely route of exposure for the general population. Typical values for the average daily intake of vinyl chloride by inhalation in urban/suburban and rural/remote areas not near emission sources are very small, since only trace levels of vinyl chloride are usually found in ambient air. Assuming that the average adult intake of air is 20 m^3/day, the average daily intake of vinyl chloride by people living in the vicinity of emission sources has been estimated to range from trace amounts to 2,100 µg (EPA 1979a, 1982f; Gordon and Meeks 1977). The majority of drinking water supplies in the United States do not contain detectable levels of vinyl chloride (EPA 1982f; Westrik et al. 1984). Based on this conclusion, it is estimated that the average daily intake of vinyl chloride by ingestion of drinking water for most people in the United States is essentially zero (at or below 0.028 µg/kg/day [EPA 1982f]). Estimates provided by EPA (1985b) indicate that 0.9% of the U.S. population is exposed to levels of vinyl chloride in drinking water ≥1 µg/L, and 0.3% of the population is exposed to levels >5 µg/L.

NOES conducted by NIOSH from 1981 to 1983 estimated that 81,314 workers employed at 3,711 plant sites were potentially exposed to vinyl chloride in the United States (NOES 1990). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to chemicals in the workplace. Exposure is believed to occur primarily through inhalation with some possible absorption through the skin (Hefner et al. 1975a). Workers that are involved in welding applications that use PVC pipes or other PVC materials may be exposed to higher levels of vinyl chloride from subsequent fumes. Airborne vinyl chloride levels of less than the detection limit of 0.05 ppm (0.13 mg/m^3) to 0.1 ppm (0.26 mg/m^3) were observed during the thermal welding of PVC pipes (Williamson and Kavanaugh 1987). Workers involved in the production of vinyl chloride or the manufacture of PVC materials have the potential to be occupationally exposed to high levels of vinyl chloride. Table 6-2 summarizes the level of vinyl chloride observed in

Table 6-2. Vinyl Chloride Levels in Five Polyvinyl Chloride Manufacturing Facilities[a]

Sample site	Number of samples	Mean (mg/m^3)	Median (mg/m^3)	Range (mg/m^3)
Outside reaction tank	4	296.30	86.25	6.19–1009.32
Reaction tank farm	18	13.60	9.97	0.18–110.59
Vinyl chloride recovery	9	9.25	5.46	0.85–33.39
Vinyl chloride shipping	3	5.98	7.38	0.85–9.71
Vinyl chloride storage tanks	6	4.97	3.03	0.60–14.25
Stripper	12	3.86	1.68	<LOD–18.62
Waste water treatment	7	3.37	3.32	0.83–6.73
Drier	11	2.62	1.55	<LOD–7.17
Control room (inside)	6	2.15	1.48	0.57–5.13
Control room (inside)	7	1.71	0.91	0.18–4.07
Polyvinyl chloride warehouse	17	1.66	1.79	<LOD–5.96
Factory perimeter	3	1.66	0.85	<LOD–3.34
Additive preparation	6	1.61	0.78	0.57–4.07
Administrative office	4	0.65	0.67	<LOD–1.27
Plastic pallet making area	1	<LOD	<LOD	<LOD

[a]Du et al. 1996

LOD = limit of detection (0.1259 mg/m^3)

five PVC manufacturing facilities located in Taiwan, and Table 6-3 provides the 8-hour time-weighted average (TWA) exposure to workers performing various job tasks (Du et al. 1996). Tank suppliers, cleaners, and PVC relievers were observed to have the highest TWA exposure since they more often came into direct contact with vinyl chloride in these job functions. In the United States, vinyl chloride is an Occupational Safety and Health Administration (OSHA) regulated substance. Current OSHA regulations impose a permissible exposure limit (PEL) of 1.0 ppm (2.6 mg/m^3) averaged over an 8-hour period or a short-term exposure of no more than 5 ppm over a 15-minute period (Cowfer and Gorensek 1997). Where concentrations cannot be lowered below the PEL of 1.0 ppm, employers must create an area with controlled access and a respirator program conforming to OSHA standards.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children are likely to be exposed to vinyl chloride via the same pathways that affect non-occupationally exposed adults; namely inhalation of ambient air and ingestion of food items or drinking water that may contain low levels of vinyl chloride. Children's plastic products such as bath toys, squeeze toys, and dolls are often made from PVC. Chewing or sucking on these toys has the potential to release any unpolymerized vinyl chloride from the object; however, no quantitative data exists regarding this potential exposure route and it is unlikely that there are significant levels of vinyl chloride in PVC-based toys. Vinyl chloride has not been detected in samples of human maternal adipose tissue, maternal blood, cord blood, or breast milk. No body burden studies that quantitatively or qualitatively identified vinyl chloride in children were located.

Table 6-3. Time-weighted Average Exposure to Workers in Polyvinyl Chloride Manufacturing Facilities[a]

Job description	Number of samples	Mean (mg/m^3)	Median (mg/m^3)	Range (mg/m^3)
Tank supplier	9	659.67	23.70	5.70–3,677.8
Polyvinyl chloride reliever	10	153.07	47.92	1.04–825.69
Tank cleaner	14	95.57	69.15	0.36–341.88
Vinyl chloride unloading	2	12.56	12.56	10.23–14.97
Safety/health specialist	4	12.04	1.74	1.19–22.87
Foreman	4	9.04	6.89	1.84–20.59
Stripper operator	3	4.51	3.37	2.33–7.82
Vinyl chloride recovery	5	4.38	4.48	0.88–5.93
Control room operator	8	4.01	3.47	1.04–10.02
Field supervisor	6	3.42	3.47	1.19–7.95
General office personnel	4	3.34	2.56	<LOD–8.18
Maintenance	3	2.69	1.76	0.85–5.49
Dryer operator	6	1.84	1.48	<LOD–4.25
Bagger and trucker	5	0.93	1.09	<LOD–1.58
Gatekeeper	2	0.93	0.93	<LOD–1.86

[a]Du et al. 1996

LOD = limit of detection (0.1259 mg/m^3)

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Individuals located near or downwind of production facilities, hazardous waste disposal sites, and landfills may be exposed to atmospheric levels of vinyl chloride higher than ambient background levels. Concentrations around 5–8 μg/m^3 (0.002–0.003 ppm) have been measured in the air above some landfills (Baker and Mackay 1985; Stephens et al. 1986). Homes near one hazardous waste site in southern California were found to contain levels as high as 1,040 μg/m^3 of vinyl chloride (0.4 ppm) (Stephens et al. 1986) and homes near another site contained levels between 2.6 and 23.4 μg/m^3 (Miller and Beizer 1985). These concentrations are several times greater than ambient air levels that are generally <1 μg/m^3 (Pratt et al. 2000). For specific levels associated with health effects, see Section 3.4. Individuals living near hazardous waste sites and landfills may also be exposed to vinyl chloride in their drinking water. Workers involved in the production or use of vinyl chloride are likely to be exposed to levels greater than the levels that the general public is exposed to (see Section 6.5).

Cigarette smoke and smoke from small cigars have been found to contain vinyl chloride at levels of 5.6–27 ng per cigarette (Hoffman et al. 1976). Therefore, people who smoke heavily may be potentially exposed to higher levels of vinyl chloride than nonsmokers.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the adverse health effects of vinyl chloride is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to ensure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of vinyl chloride.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of vinyl chloride are sufficiently well characterized to permit estimation of its environmental fate (Amoore and Hautala 1983; Cowfer and Magistro 1983; EPA 1985b; Fire 1986; HSDB 2004; IARC 1979; Lewis 1996; Lyman et al. 1982).

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI02 2004), which contains this information for 2002, became available in July of 2004. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Vinyl chloride is released primarily to the atmosphere via emissions from vinyl chloride and PVC manufacturing facilities (Hartmans et al. 1985; SRI 1990a, 1990b, 1993, 1994; TRI02 2004). The risk of exposure to vinyl chloride is highest for workers in the plastics industry and populations living near industrial areas or hazardous waste sites. Current production, use, and manufacturing methods are well described in the literature (Cowfer and Magistro 1985; HSDB 1996; IARC 1979; SRI 1990a, 1990b, 1993, 1994; TRI02 2004; USITC 1994). More current information on releases and disposal methods might assist in estimating potential exposures to vinyl chloride, particularly for populations living near hazardous waste sites.

Environmental Fate. Vinyl chloride primarily partitions to the air where it is degraded relatively quickly by photochemically produced hydroxyl radicals (Kwok and Atkinson 1994). It is removed from surface water and soils mainly by volatilization and photodegradation (EPA 1976a). Biodegradation and hydrolysis also occur (Barrio-Lage et al. 1990; Castro et al. 1992a, 1992b; Davis and Carpenter 1990; EPA 1976a), but these reactions are generally slow as compared to the volatilization rate. More information regarding the transformation and degradation in soil and water would be helpful in defining the potential pathways for human exposure.

Bioavailability from Environmental Media. Vinyl chloride can be absorbed following inhalation (Bolt et al. 1977; Krajewski et al. 1980; Withey 1976), oral (Feron et al. 1981; Watanabe et al. 1976a; Withey 1976), and to a much lesser extent, dermal exposure (Hefner et al. 1975a). These routes of

exposure may be of concern to humans because of the potential of vinyl chloride to contaminate air (Baker and MacKay 1985; EPA 1979a; Fishbein 1979; Gordon and Meeks 1977; Stephens et al. 1986; Wood and Porter 1987), water (Burmaster 1982; Cotruvo 1985; Dyksen and Hess 1982; Goodenkauf and Atkinson 1986; Stuart 1983; Westrick et al. 1984), and food (Gilbert et al. 1980; Williams 1976; Williams and Miles 1975). Information regarding the bioavailability from ingestion and dermal contact of contaminated soils would be helpful, particularly for populations living near hazardous waste sites, although vinyl chloride is not believed to be absorbed through skin.

Food Chain Bioaccumulation. Vinyl chloride can bioconcentrate to a limited extent in aquatic organisms (EPA 1982a; Freitag et al. 1985). Biomagnification of vinyl chloride in terrestrial and aquatic food chains does not appear to be important because of its high volatility and the fact that it is readily metabolized by higher-trophic-level organisms (Freitag et al. 1985; Lu et al. 1977). No data were located regarding biomagnification in terrestrial foodchains.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of vinyl chloride in contaminated media at hazardous waste sites are needed so that the information obtained on levels of vinyl chloride in the environment can be used in combination with the known body burden of vinyl chloride to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Vinyl chloride has been detected in air (Baker and Mackay 1985; EPA 1979a; Fishbein 1979; Gordon and Meeks 1977; Stephens et al. 1986; Wood and Porter 1987), water (Burmaster 1982; Cotruvo 1985; Dyksen and Hess 1982; Goodenkauf and Atkinson 1986; Stuart 1983; Westrick et al. 1984), sediment (Wang et al. 1985), and food (Gilbert et al. 1980; Williams 1976; Williams and Miles 1975). Intake data for the general population from the various media are available (EPA 1979a, 1985b; Gordon and Meeks 1977; Westrick et al. 1984). Data on levels of vinyl chloride in soils are needed. Site-specific data on concentrations of vinyl chloride in air, soil, and water would be helpful in estimating the risk of exposure for populations living in the vicinity of hazardous waste sites. Also, current data on the extent of release (if any) of vinyl chloride from PVC pipes and from car interiors are needed to estimate the risk of exposure of the general population.

Exposure Levels in Humans. Vinyl chloride has been detected in exhaled breath of humans (Baretta et al. 1969; Conkle et al. 1975), but no other body burden studies are available. More information on exposure levels for populations living in the vicinity of hazardous waste sites would be helpful. This information is necessary for assessing the need to conduct health studies on these

populations. It is noted that it is difficult to directly analyze for vinyl chloride in humans, which may limit the practicality of conducting these tests.

Exposures of Children. No data exist regarding the levels of vinyl chloride in children. Children are exposed to vinyl chloride by the same pathways that affect adults; inhalation of ambient air and the ingestion of foods or drinking water. It would be useful to determine if there exists any free unpolymerized vinyl chloride that can be extracted from PVC children's toys. Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for vinyl chloride were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2004) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1.

John Furgeson (University of Washington) is investigating the *in-situ* bioremediation of chlorinated aliphatics (including vinyl chloride) at hazardous waste sites by anaerobic reductive transformation pathways. Josse Fabien and Zhou Rongnong of the University of Marquette (Milwaukee, Wisconsin) are attempting to characterize and design polymer-coated chemical sensors for the direct, rapid, *in-situ* monitoring of vinyl chloride and other hazardous constituents in water. Envirogen Incorporated (R.J. Steffan, Principal Investigator) is attempting to develop specialized bio-catalysts that will aid in the remediation of aquifers contaminated with chlorinated volatile organic compounds, including vinyl chloride. It is hypothesized that bioaugmentation of contaminated aquifers with microorganisms capable of greater sediment penetration, continuous enzyme expression, and prolonged activity will significantly improve *in situ* bioremediation efforts. Stuart Strand (University of Washington) is studying the ability of several plant strains to take up and transform various chlorinated hydrocarbons, including vinyl chloride, in order to aid in remediation strategies. Karla Thrall (Oregon Health and Science University) is studying

the potential for human exposure to vinyl chloride and other VOC near Superfund sites. Exposure assessment studies will be conducted with volunteers using a novel real-time breath analysis system to determine the uptake of any of the nine potential contaminants of study from tap water by each of three routes: inhalation, ingestion, and dermal contact.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring vinyl chloride, its metabolites, and other biomarkers of exposure and effect to vinyl chloride. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

The analytical method used to analyze for the presence of vinyl chloride in biological samples is separation by gas chromatography (GC) combined with detection by mass spectrometry (MS), flame ionization detector (FID), or electron capture detector (ECD). Vinyl chloride and/or its metabolite, thiodiglycolic acid, have been detected in breath, urine, blood, and tissues. Breath samples can be concentrated by cryogenic trapping. The two methods most commonly used to prepare liquid and solid samples are concentration by a purge-and-trap technique or headspace analysis. Concentration not only increases the sensitivity but, also in certain instances, may decrease the sample separation time prior to quantitation. Details of commonly used analytical methods for several types of biological samples are presented in Table 7-1.

Vinyl chloride was determined in exhaled air by concentration with a multistage cryogenic trapping system followed by thermal desorption using GC/FID, GC/ECD, and GC/MS (Conkle et al. 1975). Sensitivity is in the low-ppb range. The authors of this study noted that the reproducibility of the subject/sampling system was inconclusive; a larger experimental population is needed for its demonstration. The quantitative data reflected considerable scatter, apparently indicating the variability of the biological system and the trace amounts of the compound. The additional requirement for long-term coupling (30–60 minutes) of the sampling system to the subject probably limits the method to industrial health applications, with relatively robust subjects (Conkle et al. 1975). Baretta et al. (1969)

Table 7-1. Analytical Methods for Determining Vinyl Chloride in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Breath	Breath collected in pipets lined with Saran® film; direct injection into gas chromatograph	GC/FID	NR	NR	Baretta et al. 1969
Breath	Cyrogenic trapping of expired air; thermal desorption into gas chromatograph	GC/FID, GC/ECD, and GC/MS	NR	NR	Conkle et al. 1975
Urine	Acidified and desiccated overnight; add methanol; derivatize with diazamethane; add ion-exchange resin	GC/MS	50 ng/mL	NR	Müller et al. 1979
Urine	Internal standard added to urine; acidification and ethyl acetate extraction; evaporation of solvent; addition of N-trimethylsilyldiethyl-amine in pyridine (1:1); injection into gas chromatograph	GC/FID, GC/MS	10 mg/L	NR	Draminski and Trojanowska 1981
Blood and tissues	Extraction in ethanol-water mixture; incubation, injection into gas chromatograph	GC/FID	5 ng/mL blood	75–79%	Zuccato et al. 1979
	Tissue preparation also includes freezing and homogenization before the extraction procedure		30 ng/g tissue	76–92%	

GC/ECD = gas chromatography/electron capture detector; GC/FID = gas chromatography/flame ionization detector; GC/MS = gas chromatography/mass spectrometry; NR = not reported

monitored exposure to vinyl chloride by breath analysis. The breath samples were collected in pipets with plastic caps lined with six layers of Saran film identical to that used for the construction of Saran air sampling bags. Aliquots were drawn from the pipets and injected directly into a gas chromatograph equipped with FID. One limitation of this method is its reduced ability to detect vinyl chloride when air concentrations in the workplace are below 50 ppm.

Vinyl chloride has been measured in rat blood and tissues using headspace GC/FID (Zuccato et al. 1979). In headspace analysis, the gaseous layer above the sample is injected into the gas chromatograph. Sample preparation steps for rat blood and tissues involve extraction in an ethanol-water mixture, incubation, and direct injection into the gas chromatograph. Sample preparation for tissues includes an extra step involving freezing and homogenization before the extraction procedure. The recovery ranged from about 75 to 92%. The method is sensitive to 5 ng/mL vinyl chloride in blood and 30 ng/g in tissues.

Müller et al. (1979) employed GC/MS as a selective biomonitoring method for the quantitative measurement of thiodiglycolic acid, a urinary metabolite of vinyl chloride. They reported a sensitivity of 50 ng/mL. Precision was generally good. These investigators noted that some thiodiglycolic acid has been found in supposedly unexposed subjects. Therefore, exposure to low levels of vinyl chloride could be masked by background metabolic levels within normal limits. This may limit the application of biological monitoring for the measurement of vinyl chloride following low-level exposure (Müller et al. 1979; van Sittert and de Jong 1985). In a study by Jedrychowski et al. (1984), urinary excretion of thiodiglycolic acid was determined using GC/FID. The urine was extracted twice with ethyl acetate prior to analysis. No recovery data were given for this method.

7.2 ENVIRONMENTAL SAMPLES

Analysis of environmental samples is similar to that of biological samples. The most common methods used to detect vinyl chloride in environmental samples are GC/MS, GC/ECD, and GC/FID. Concentration of samples is usually done by sorption on solid sorbent for air and by the purge-and-trap method for liquid and solid matrices. Alternatively, headspace above liquid and solid samples may be analyzed without preconcentration. Details of commonly used analytical methods for several types of environmental samples are presented in Table 7-2.

The primary method of analyzing vinyl chloride in air is GC combined with either MS, ECD, or FID. Air samples are usually pumped through a sample collection column with Tenax-GC, coconut activated

Table 7-2. Analytical Methods for Determining Vinyl Chloride in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Occupational air	Vinyl chloride in air adsorbed in activated carbon trap and desorbed by carbon disulfide	GC/FID	0.04 µg per sample	94% at 1–64 mg/m^3 (0.00039–0.025 ppb)	NIOSH 1994a
Ambient indoor and outdoor air	Air containing vinyl chloride passed through activated carbon trap and desorbed by dichloromethane or carbon	GC/FID	5 ppb	NR	IARC 1978
Air	Adsorption onTenax®-GC or SKC® Carbon, then thermal desorption	GC/MS	0.33 ppb	NR	Krost et al. 1982
Air	Air prefiltered by $Na_2S_2O_3$-treated glass fiber filter was passed through spherocarb adsorbent cartridge and thermally desorbed	GC/FID, GC/MS, GC/ECF	0.005 ppb	NR	Harkov et al. 1983, 1984
Automobile exhaust	Exhaust samples contained in aluminized plastic bags	GC/FID	0.02 ppm	NR	Hasanen et al. 1979
Air	Trapped in cold Tenax®-GC trap; thermal desorption	GC/FID	NR	89.6% at 6 ppb; 100% at 60 ppb	Ives 1975
Air	Sample collected in pressurized canister is passed through a freezeout loop and subsequently heated	GC/ECD	0.01 ppb	NR	Harsch et al. 1979; Rasmussen et al. 1977
Air	Sample collected in polyester-coated plastic bags concentrated by freezeout and subsequently heated	GC/FID	0.4 ppb	NR	McMurray and Tarr 1978
Drinking water	Samples collected in serum reaction bottles; purge and trap technique	GC/HSD, GC/MS	NR	NR	Dressman and McFarren 1978
Drinking water and waste water	Purge and trap in Tenax®-GC; thermal desorption	GC/HSD, GC/MS (EPA Methods 601 and 624)	0.18 ppb (HSD)	102% at 0.8–32.3 ppb	APHA 1985; EPA 1982d

Table 7-2. Analytical Methods for Determining Vinyl Chloride in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Groundwater, liquid and solid matrices	Purge at 45 °C and trap in Tenax®-GC; thermal desorption	GC/HSD (EPA Method 8010)	0.18 ppb	102% at 0.82–32.3 ppb	EPA 1982e
Water	Purge into Carbosieve™ S III; desorption with CS_2 and bromine derivation	GC/ECD	0.0004 ppb	98.9% at 0.00625–62.5 ppb	Wittsiepe et al. 1993
Drinking water	Purge and trap in Tenax®-GC; thermal desorption	GC/Hall detector, GC/PID (EPA Methods 502.2 and 524.2)	0.04 ppb (Hall detector); 0.02 ppb (PID)	100–119% at 5–10 ppb	Reding 1987
Migration of monomer into drinking water from PVC pipes	Small section put in water in sealed serum vial for a number of days at 20 °C; solution directly injected into gas chromatograph	GC/FID	NR	NR	Ando and Sayato 1984
Water	Sample ins sealed vial is equilibrated at constant temperature; headspace gas injected into gas chromatograph	GC/FID	<1 ppb	NR	IARC 1978
Landfill gas	Gas from landfill sites sampled by PTFE tubing inside drive-in piezometers was adsorbed in Tenax®-GC or Porapak®, a sorbent; trapped sample desorbed and concentrated in liquid N_2-cooled loop and flash desorbed	GC/MS	0.04–0.8 ppm	NR	Young and Parker 1984
Sediment and oyster	Homogeneous sample mixed with water and vinyl chloride purged into a closed loop injected into gas chromatograph	GC/ECD	2 ng/g (sediment); 4 ng/g (oyster)	NR	Wang et al. 1985
Landfill gas	Sample collected in 2-L evacuated glass bulb; gas directly injected into gas chromatograph	GC/FID	NR	NR	Wood and Porter 1987

Table 7-2. Analytical Methods for Determining Vinyl Chloride in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food (orange drink, wine, olive oil)	Sample sealed in vials and equilibrated at 40 °C for 2 hours; injected into gas chromatograph	GC/FID	NR	NR	Chudy and Crosby 1977
Foodstuffs	Sample sealed in vials and equilibrated at 40 °C for a minimum of 2 hours; headspace gas injected into gas chromatograph	GC/FID	1–5 ppb	NR	IARC 1978

CS_2 = carbon disulfide; EPA = Environmental Protection Agency; GC/ECD = gas chromatography/electron capture detector; GC/FID = gas chromatography/flame ionization detector; GC/HSD = gas chromatography/halogen specific detector; GC/MS = gas chromatography/mass spectrometry; GC/PID = gas chromatography/photoionization detector; HSD = halogen specific detector; N_2 = nitrogen; $Na_2S_2O_3$ = sodium thiosulfate; NR = not reported; PID = photoionization detector; PTFE = polytetrafluorethylene; PVC = polyvinyl chloride

charcoal, or spherocarb (a carbon molecular sieve material) as the most common adsorbents. Several authors have noted that Tenax-GC displays poor retention for vinyl chloride when the compound is present in the very low-ppb range (Bozzelli and Kebbekus 1979; Krost et al. 1982; McMurry and Tarr 1978). Vinyl chloride is thermally desorbed from the collection column and concentrated on a cryogenic trapping column located on the gas chromatograph. Vapors are heat-released from the trapping column directly to the gas chromatograph (Bozzelli and Kabbekus 1979; Krost et al. 1982). Grab samples of air can also be obtained and preconcentrated on a cryogenic column (Rasmussen et al. 1977). The limit of detection for GC/MS and GC/ECD is in the sub-ppb range (Bozzelli and Kebbekus 1979; Harsch et al. 1979; Krost et al. 1982; Rasmussen et al. 1977). Accuracy is generally good (Bozzelli and Kebbekus 1979). With careful technique, precision is adequate, ranging from 5 to 20% (Bozzelli and Kebbekus 1979; McMurray and Tarr 1978).

Trace amounts of vinyl chloride in air and water were detected employing GC/ECD after derivatization to 1,2-dibromochloroethane (Wittisiepe et al. 1990, 1993). Air samples were taken by drawing a known volume directly through an ice-cooled adsorption tube. Water samples were purged with an inert gas before being drawn through the adsorption tube. The tubes were eluted with carbon disulfide, and the vinyl chloride was derivatized with bromine water to form 1,2-dibromochloroethane. This derivatization technique is used for enhancement of sensitivity with GC/ECD. The derivative was determined by capillary GC with ECD. The detection limits for air and water samples are 50 ng/m^3 and 0.4 ng/L (0.4 parts per trillion), respectively. Results from recovery experiments with dosed water indicated that accuracy was good.

Vinyl chloride can be detected in drinking water, groundwater, waste water, and leachate from solid waste. Analysis of vinyl chloride is done by purge-and-trap or headspace GC. The primary analytical method is separation by GC combined with MS, ECD, FID, Hall's electrolytic conductivity detector (HECD), or another type of halogen specific detector (HSD). In most methods, vinyl chloride is liberated from the liquid matrix by purging with an inert gas and concentrated by trapping on a suitable solid sorbent. Vinyl chloride is thermally desorbed and backflushed onto the column of the gas chromatograph with an inert gas. Detection of vinyl chloride is generally achieved using HECD, HSD, or MS (APHA 1985; EPA 1982d, 1982e; IARC 1978; Reding 1987). The limit of detection is in the sub-ppb range for halogen specific detectors (APHA 1985; EPA 1982d, 1982e) and in the low-ppb range for MS (EPA 1982d). Accuracy is >98% and precision ranges from 11 to 25% for GC/HECD and GC/MS (EPA 1982d).

EPA has made improvements in methods for measuring volatile organic chemicals. The major change is the use of smaller sample volumes allowed by increased use of capillary gas chromatographic columns. Capillary columns provide better resolution, minimum detection limits, and less column bleed than packed columns (Reding 1987).

Vinyl chloride has been measured in sediment using GC/ECD with sensitivity in the low-ppb range. Accuracy and precision data were not provided in the report (Wang et al. 1985). No information on analysis of vinyl chloride in soil was located. GC/HSD of headspace gases is the EPA-recommended method for solid matrices with sensitivity in the sub-ppb range. Accuracy (101.9%) is good and precision (11.4%) is adequate (EPA 1982d). Vinyl chloride levels in food have been determined using GC/FID. GC analysis by headspaces gases is a common method for testing foods, with sensitivity in the low-ppb range (IARC 1978).

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the adverse health effects of vinyl chloride is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to ensure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such adverse health effects) of vinyl chloride.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Methods are available for measuring vinyl chloride and/or its metabolite, thiodiglycolic acid, in breath, urine, blood, and tissue (Baretta et al. 1969; Conkle et al. 1975; Draminski and Trojanowska 1981; Müller et al. 1979; Zuccato et al. 1979). These methods are sensitive for measuring levels at which adverse health effects might occur, and for measuring higher background levels that might be found in specific populations known to be exposed to elevated levels of vinyl chloride (e.g., workers in the plastics industry and individuals living in the vicinity of hazardous waste sites). Measurement of urinary thiodiglycolic acid can be used as an indicator of vinyl chloride intake as long as individual variability in metabolism (due to such factors as liver disease, use of drugs, and alcohol intake) can be accounted for (Hefner et al. 1975b; Müller et al. 1979). Exposure to vinyl chloride at concentrations below 1–5 ppm could be masked by background metabolic levels of thiodiglycolic acid within normal limits (Müller et al. 1979). Also, the formation of thiodiglycolic acid is not unique to vinyl chloride exposure (Norpoth et al. 1986; Pettit 1986). The methods are generally reliable, although increased precision for most methods would increase reliability. Background levels for the general population are ill defined (EPA 1985b). Further research on the relationship between low-level exposure and levels of vinyl chloride in biological media would be helpful in assessing the risks and adverse health effects of chronic, low-level exposure.

Effect. Existing methods are sensitive for measuring levels of vinyl chloride and its metabolite, thiodiglycolic acid, in individuals affected by exposure to very high levels of vinyl chloride (Baretta et al. 1969; Conkle et al. 1975; Draminski and Trojanowska 1981; Müller et al. 1979; Zuccato et al. 1979). Also, methods are available to detect DNA adducts produced by the reaction of vinyl chloride metabolites with DNA (Eberle et al. 1989; Young and Santella 1988). These DNA adducts are specific indicators of vinyl chloride's genotoxic potential. These methods, however, are not sufficiently sensitive to determine the genotoxic effects resulting from low-level exposure. Correlations between levels detected in biological tissues and fluids and specific observed effects for lower levels of exposure have not been established. Additional research in this area would allow better assessment of existing methods and would help in defining areas in which improvements are needed.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Existing methods for determining vinyl chloride in air (Harkov et al. 1983, 1984; Harsch et al. 1979; Hasanen et al. 1979; IARC 1978; Ives 1975; Krost et al. 1982; McMurry and Tarr 1978; NIOSH

1994a; Rasmussen et al. 1977) and water (Ando and Sayato 1984; APHA 1985; Dressman and McFarren 1978; EPA 1982d, 1982e; IARC 1978; Reding 1987), the media of most concern for human exposure, are sensitive, reproducible, and reliable for measuring background levels in the environment. Research investigating the relationship between levels measured in air and water and observed adverse health effects could increase our confidence in existing methods and/or indicate where improvements are needed. Methods specifically relating to the analysis of vinyl chloride in soils were not located. EPA does, however, have sensitive and reliable methods for determining the concentration of vinyl chloride in soil matrices (EPA 1982e), which include contaminated soils.

7.3.2 Ongoing Studies

Eltron Research Incorporated (Principal Investigator, Thomas Ross) is developing a direct-reading personal monitor for detecting vinyl chloride in workplace air (FEDRIP 2004).

8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding vinyl chloride in air, water, and other media are summarized in Table 8-1.

ATSDR has derived three MRL values for vinyl chloride. An acute-duration inhalation MRL of 0.5 ppm was derived for vinyl chloride based on a NOAEL for developmental effects for mice (John et al. 1977, 1981). An intermediate-duration inhalation MRL of 0.03 ppm was derived for vinyl chloride based on a LOAEL of 10 ppm for increased incidences of hepatic centrilobular hypertrophy in rats (Thornton et al. 2002). A chronic-duration oral MRL of 0.003 mg/kg/day was derived for vinyl chloride based on a human equivalent NOAEL for liver cell polymorphism in rats (Til et al. 1983, 1991).

EPA (IRIS 2004) has derived an RfD of 0.003 mg/kg/day for vinyl chloride, based on a NOAEL for liver cell polymorphism in rats administered vinyl chloride in the diet for a lifetime (Til et al. 1983, 1991).

EPA (IRIS 2004) has derived an RfC of 0.1 mg/m^3 (0.04 ppm) for vinyl chloride, based on route-to-route extrapolation (using PBPK modeling) from a NOAEL for liver cell polymorphism in rats administered vinyl chloride in the diet for a lifetime (Til et al. 1983, 1991).

The FDA is responsible for regulating vinyl chloride as an indirect food additive. With regard to components of coatings, paper, and paperboard, the FDA states that when vinyl chloride is copolymerized with certain other substances, it is a safe food-contact surface. The amount of vinyl chloride content permitted varies depending on the nature of the polymer and its use (FDA 1994).

Table 8-1. Regulations and Guidelines Applicable to Vinyl Chloride

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 1[a]	IARC 1987
WHO	Drinking water guideline (10^{-6} cancer risk)	0.5 µg/L	WHO 1996
	Air quality guideline (10^{-6} cancer risk)	1 µg/m^3	WHO 2000
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	1 ppm	ACGIH 2003
EPA	Hazardous air pollutant		EPA 2004k 42USC7412
	Regulated toxic substances and threshold quantities for accidental release prevention	10,000 pounds	EPA 2004a 40CFR68.130
NIOSH	REL (10-hour TWA)	Potential occupational carcinogen	NIOSH 2004
	IDLH	No data	
OSHA	PEL for general industry		OSHA 2004a 29CFR1910.1017
	8-hour TWA	1 ppm	
	15-minute TWA	5 ppm	
	PEL for shipyard industry		OSHA 2004b 29CFR1915.1017
	8-hour TWA	1 ppm	
	15-minute TWA	5 ppm	
	PEL for construction industry		OSHA 2004c 29CFR1926.1117
	8-hour TWA	1 ppm	
	15-minute TWA	5 ppm	
b. Water			
	Drinking water standards and health advisories		EPA 2004c
	1-Day HA for a 10-kg child	3.0 mg/L	
	10-Day HA for a 10-kg child	3.0 mg/L	
	DWEL	0.1 mg/L	
	10^{-4} Cancer risk	0.002 mg/L	
	Drinking water standards	0.002 mg/L	EPA 2004j 40CFR141.32
	MCL	0.002 mg/L	EPA 2004i 40CFR141.61
	MCLG	Zero	EPA 2004g 40CFR141.50
c. Food			
FDA	Bottled water	0.002 mg/L	FDA 2003a 21CFR165.110

Table 8-1. Regulations and Guidelines Applicable to Vinyl Chloride

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	Drug products withdrawn or removed from the market for reasons of safety or effectiveness	All aerosol drug products containing vinyl chloride	FDA 2003c 21CFR216.24
FDA	Indirect food additive for use only as a component of adhesives		FDA 2003b 21CFR175.105
d. Other			
ACGIH	Carcinogenicity classification	A1[b]	ACGIH 2003
EPA	Carcinogenicity classification	Group A[cd]	IRIS 2004
	Oral slope factor		
	Continuous lifetime exposure during adulthood	$7.2x10^{-1}$ $(mg/kg/day)^{-1}$	
	Continuous lifetime exposure from birth	1.4 $(mg/kg/day)^{-1}$	
	Drinking water unit risk		
	Continuous lifetime exposure during adulthood	$2.1x10^{-5}$ $(\mu g/L)^{-1}$	
	Continuous lifetime exposure from birth	$4.2x10^{-5}$ $(\mu g/L)^{-1}$	
	Inhalation unit risk		
	Continuous lifetime exposure during adulthood	$4.4x10^{-6}$ $(mg/m^3)^{-1}$	
	Continuous lifetime exposure from birth	$8.8x10^{-6}$ $(mg/m^3)^{-1}$	
	RfC RfD	$1x10^{-1}$ mg/m^3 $3x10^{-3}$ mg/kg/day	
	Community right-to-know; release reporting; effective date	01/01/1987	EPA 2004m 40CFR372.65
	Hazardous waste identification	U043	EPA 2004d 40CFR261, Appendix VIII
	Superfund; designated as a hazardous substance pursuant to Section 307(a) of the Clean Water Act, Section 112 of the Clean Air Act, and Section 3001 of RCRA; reportable quantity	1 pound	EPA 2004b 40CFR302.4
NTP	Carcinogenicity classification	Known to be a human carcinogen	NTP 2002
STATE			
a. Air			
California	Acute inhalation reference exposure level	$2x10^5$ mg/m^3	
b. Water			
	Drinking water guidelines and standards		HSDB 2004
Arizona		0.015 µg/L	

Table 8-1. Regulations and Guidelines Applicable to Vinyl Chloride

Agency	Description	Information	Reference
STATE *(cont.)*			
California	MCL	0.5 µg/L	
	Public Health Goal	0.05 µg/L	
Connecticut		2.0 µg/L	
Florida		1.0 µg/L	
Maine		0.15 µg/L	
Minnesota		0.2 µg/L	
New Jersey		2.0 µg/L	
Wisconsin		0.2 µg/L	
c. Food			
No data			
d. Other			
No data			

[a]Group 1: Carcinogenic to humans.
[b]Group A1: Confirmed human carcinogen.
[c]Group A: Human carcinogen; according to EPA Risk Assessment Guidelines (EPA 1986).
[d]Vinyl chloride a known human carcinogen by the inhalation and oral route of exposure and is also considered highly likely to be carcinogenic by the dermal route of exposure (EPA 1996).

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HA = Health Advisory; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; RfC = reference concentration; RfD = reference dose; STEL = short-term exposure limit; TLV = threshold limit values; TWA = time-weighted average; USC = United States Codes; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD10 would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube; also, organisms isolated and maintained in culture.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration(Lo) (LC_{Lo})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration(50) (LC_{50})—A calculated concentration of a chemical in air or water to which exposure for a specific length of time is expected to cause death in 50% of a defined population of experimental animals or fish and other aquatic species.

Lethal Dose(Lo) (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose(50) (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time(50) (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly

describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a specified period of time, generally an 8-hour workday or 40-hour workweek.

Toxic Dose(50) (TD50)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicodynamic—The interaction of chemicals with target tissues in living organisms to produce toxicity

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances by determining an appropriate point-of departure (i.e., no-observed-adverse-effect level or a benchmark dose) and then applying uncertainty factors. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Vinyl Chloride
CAS Number: 75-01-4
Date: September 12, 2004
Profile Status: Final Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 28
Species: Rat

Minimal Risk Level: 0.5 [ ] mg/kg/day [X] ppm

References:

John JA, Smith FA, Leong BKJ, et al. 1977. The effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats, and rabbits. Toxicol Appl Pharmacol 39:497-513.

John JA, Smith FA, Schwetz BA. 1981. Vinyl chloride: Inhalation teratology study in mice, rats, and rabbits. Environ Health Perspect 41:171-177.

Experimental design: CF-1 mice were exposed to vinyl chloride at concentrations of 0, 50, or 500 ppm for 7 hours/day on gestational days 6–15 (John et al. 1977, 1981). Concurrent control groups were used, one for each dose level. Control groups were sham-exposed to filtered room air. Exposure was conducted in chambers of 3.7 m^3 volume under dynamic conditions. Animals were observed daily for clinical signs, and maternal body weights were determined several times during gestation. Animals were euthanized on gestational day 18 by carbon dioxide inhalation. Maternal liver weight was determined and uterine horns were examined. Fetuses were weighed, measured (crown-rump length), sexed, and subjected to gross and histopathological examinations.

Effects noted in study and corresponding doses: No adverse maternal or fetal effects were noted at 50 ppm, with the exception of a slight increase ($p<0.05$) in crown-rump length that was not observed at 500 ppm. The 50-ppm exposure level is considered to be a NOAEL for maternal and developmental toxicity. At the LOAEL of 500 ppm, delayed ossification ($p<0.05$) was observed. An increase in resorptions at 500 ppm was considered to have been within historical control limits. Significant changes in percentage resorption, litter size, and fetal body weight would not have been observed at 500 ppm if comparison had been made to the other control group. There was frank maternal toxicity at 500 ppm (17% death). The limited number and spacing of dose group precludes the use of benchmark dose modeling for determination of the point-of-departure for the MRL.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL [ ] benchmark dose

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustment
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: The intermittent exposure duration of 7 hours/day was duration-adjusted to continuous exposure according to the following equation:

Duration-adjusted NOAEL = NOAEL (50 ppm) x 7 hours/24 hours per day = 15 ppm.

Following EPA (1994g) methodology, the human equivalent concentration ($NOAEL_{HEC}$) for an extrarespiratory effect produced by a category 3 gas, such as vinyl chloride, is calculated by multiplying the duration-adjusted animal NOAEL by the ratio of the blood:gas partition coefficients in animals and humans [$(H_{b/g})_A / H_{b/g})_H$]. Since the partition coefficient in mice is greater than that in humans, as seen in Table 3-3, a default value of 1 is used for the ratio and the duration-adjusted animal NOAEL is equivalent to the $NOAEL_{HEC}$. A total uncertainty factor of 30 (3 for extrapolation from mice to humans using a dosimetric adjustment and 10 for human variability) was applied to the $NOAEL_{HEC}$.

The acute-duration inhalation MRL = duration-adjusted $NOAEL_{HEC}$ (15 ppm) ÷ 30 (UF) = 0.5 ppm.

Other additional studies or pertinent information which lend support to this MRL: Delayed ossification (500 ppm, the lowest concentration tested) was the only developmental effect observed in a rabbit developmental study (John et al. 1977/ 1981).

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Vinyl Chloride
CAS Number: 75-01-4
Date: September 12, 2004
Profile Status: Final Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 39
Species: Rat

Minimal Risk Level: 0.03 [ ] mg/kg/day [X] ppm

Reference: Thornton SR, Schroeder RE, Robison RL, et al. 2002. Embryo-fetal developmental and reproductive toxicology of vinyl chloride in rats. Toxicol Sci 68:207-219.

Experimental design: Groups of male and female Sprague-Dawley rats (30/sex/group) were exposed to vinyl chloride vapor concentrations of 0, 10, 100, or 1,100 ppm, 6 hours/day for 10 weeks prior to mating and during a 3-week mating period. F_0 males were exposed during the gestational period and sacrificed following the completion of parturition. F_0 females were exposed during gestation and lactation (with the exception of a break in exposure from gestation day 21 through postnatal day 4 to allow for delivery of litters). All F_0 rats were observed twice daily for clinical signs. Body weights and food consumption were monitored. F_1 litters were examined for live and dead pups and on lactation day 4, litters were culled to eight pups (equal numbers of male and female pups where possible). All F_0 female rats (including those that did not produce offspring) were sacrificed after the F_1 rats had been weaned. Reproductive tissues, adrenal glands, brain, kidneys, liver, lungs, spleen, thymus, mammary glands, nasal tissues, pituitary, and trachea from each of the F_0 rats were individually weighed and subjected to histopathologic examinations. At weaning, 15 male and female F_1 rats/group were selected for gross and microscopic examinations. Other F_1 rats were randomly selected to form groups of 30/sex/group, and these F_1 rats were subjected to the same treatment as the F_0 rats during the production of an F_2 generation. At weaning, 15 male and female F_2 rats/group were subjected to gross and microscopic examinations. Sperm parameters were assessed in 15 F_0 and 15 F_1 male rats of each exposure group.

Effects noted in study and corresponding doses: Absolute and relative mean liver weights were significantly increased at all exposure levels in F_0 males and in 100- and 1,100-ppm F_1 males. Slight centrilobular hypertrophy, considered to be a minimal adverse effect, was noted in the livers of all 1,100-ppm male and female F_0 and F_1 rats, most 100-ppm male and female F_0 and F_1 rats, and in 2/30 and 6/30 of the 10-ppm F_0 and F_1 female rats, respectively (see Table A-1). No incidences of centrilobular hypertrophy were found in any of the control rats. Compared to an incidence of 0/30 for this lesion in controls, the incidence of 6/30 in the 10-ppm F_1 female rats exceeded the level of statistical significance ($p<0.05$ according to Fisher's Exact Test performed by ATSDR).

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] LEC_{10} from benchmark dose modeling

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustment
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.
If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:
The incidence data for centrilobular hypertrophy in the male and female F_0 and F_1 rats exposed to vinyl chloride by inhalation, 6 hours/day for 10 weeks prior to mating and during mating, gestation, and lactation (Thornton et al. 2002) are shown in Table A-1.

Table A-1. Incidences of F_0 And F_1 Male and Female With Centrilobular Hypertrophy in the Liver Following Inhalation Exposure to Vinyl Chloride Vapors for 6 Hours/Day for 10 Weeks Prior to Mating and During Mating and Gestation (Males and Females) and Lactation (Females)

	Exposure concentration (ppm)			
	0	10	100	1,100
F_0 males	0/30	0/30	15/30*	30/30*
F_0 females	0/30	2/30	26/30*	30/30*
F_1 males	0/30	0/30	19/30*	30/30*
F_1 females	0/30	6/30*	30/30*	30/30*

*Statistically significantly ($p<0.05$) different from controls according to Fisher's Exact Test performed by ATSDR.

Source: Thornton et al. (2002)

All dichotomous models in the Benchmark Dose Software (BMDS version 1.3.2) were fit to the incidence data for centrilobular hypertrophy in the liver of the F_1 female rats, which had also been exposed via their mothers during pre- and post-natal development. The lower 95% confidence limit (LEC_{10}) of a 10% extra risk (EC_{10}) for hepatic centrilobular hypertrophy was selected as the benchmark response for the point of departure. The Quantal Quadratic model provided the best fit as assessed by a chi-square goodness-of-fit test and the Aikake's Information Criteria (AIC) (Table A-2). Therefore, the LEC_{10} value of 5 ppm, derived from the Quantal Quadratic model, was selected as the point of departure for calculating an intermediate-duration inhalation MRL (see Table A-2 and Figure A-1).

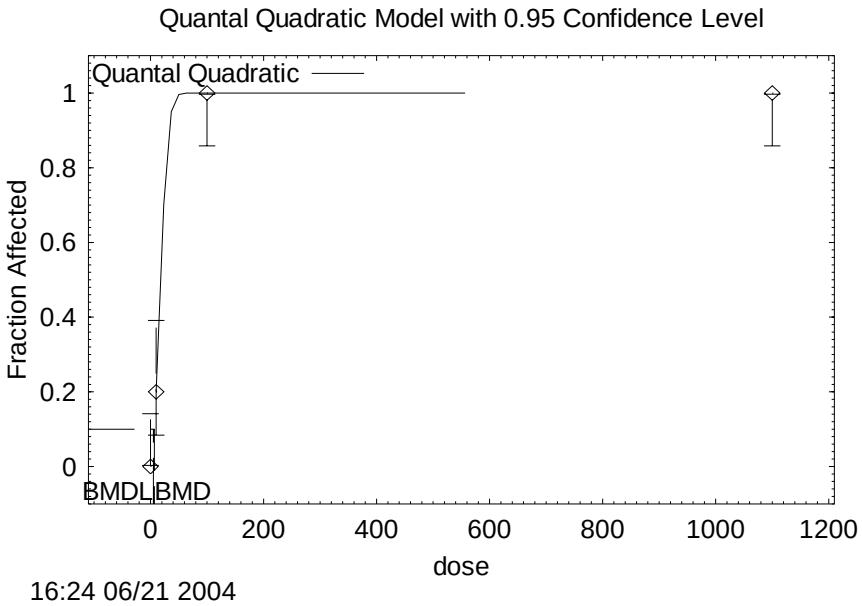
Table A-2. Modeling Results for the Incidence of F_1 Female Rats with Centrilobular Hypertrophy in the Liver Following Inhalation Exposure to Vinyl Chloride Vapors for 6 Hours/Day for 10 Weeks Prior to Mating and During Mating, Gestation, and Lactation, and Exposed via their Mothers During Pre- and Postnatal Development

Model	EC_{10} (ppm)	LEC_{10} (ppm)	χ^2 p-value	AIC
Gamma[a]	7.78	3.15	1.00	34.02
Logistic	8.75	6.15	1.00	32.05
Log-logistic[b]	9.12	5.22	1.00	34.02
Multi-stage[c]	6.35	3.44	undefined	36.02
Probit	9.11	5.69	1.00	34.02
Log-probit[b]	8.56	5.09	1.00	34.02
Quantal linear	3.03	2.05	0.53	35.28
Quantal quadratic	**6.87**	**5.08**	**1.00**	**32.02**
Weibull[a]	6.68	3.03	1.00	34.02

[a]Restrict power >=1
[b]Slope restricted to >1
[c]Restrict betas >=0; Degree of polynomial=3

Source: Thornton et al. 2002

Figure A-1. Benchmark Dose Model Results for the Incidence of Female F1 Rats with Centrilobular Hypertrophy Following Exposure to Vinyl Chloride by Inhalation, 6 Hours/Day for 10 Weeks Prior to Mating and During Mating, Gestation, and Lactation, and Exposed Via their Mothers During Pre- and Postnatal Development



The intermittent exposure duration of 6 hours/day was duration-adjusted to continuous exposure according to the following equation:

Duration-adjusted LEC_{10} = LEC_{10} (5 ppm) x 6 hours/24 hours per day = 1.25 ppm; (rounded to 1.0 ppm).

Following EPA (1994g) methodology, the human equivalent concentration (LEC_{10HEC}) for an extrarespiratory effect produced by a category 3 gas, such as vinyl chloride, is calculated by multiplying the duration-adjusted animal LEC_{10} by the ratio of the blood:gas partition coefficients in animals and humans [$(H_{b/g})_A$ / $H_{b/g})_H$]. Since the partition coefficient in mice is greater than that in humans, as seen in Table 3-3, a default value of 1 is used for the ratio and the duration-adjusted animal LEC_{10} is equivalent to the LEC_{10HEC}. Several physiologically-based pharmacokinetic (PBPK) models are available for vinyl chloride; however, none of these models included an evaluation of exposure during mating, gestation, or lactation. Therefore, PBPK models could not be used to calculate a LEC_{10HEC} from the Thornton et al. (2002) study. A total uncertainty factor of 30 (3 for extrapolation from mice to humans using a dosimetric adjustment and 10 for human variability) was applied to the $NOAEL_{HEC}$.

The intermediate-duration inhalation MRL = LEC_{10HEC} (1.0 ppm) ÷ 30 = 0.03 ppm.

Other additional studies or pertinent information which lend support to this MRL: Liver enlargement and/or histopathological changes have been noted in a number of intermediate-duration inhalation studies in animals (Bi et al. 1985; Lester et al. 1963; Schaffner 1978; Sokal et al. 1980; Torkelson et al. 1961; Wisniewska-Knypl et al. 1980). The studies by Thornton et al. (2002) and Bi et al. (1985) show these effects at a somewhat lower dosage. Additional support comes from a study citing immunostimulation in mice at 10 ppm (Sharma and Gehring 1979).

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Vinyl Chloride
CAS Number: 75-01-4
Date: September 12, 2004
Profile Status: Final Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 5
Species: Rat

Minimal Risk Level: 0.003 [X] mg/kg/day [ ] ppm

References:

Til HP, Immel HR, Feron VJ. 1983. Lifespan oral carcinogenicity study of vinyl chloride in rats. Final report. Civo Institutes, TNO. Report No. V 93.285/291099.

Til HP, Feron VJ, Immel HR. 1991. Lifetime (149-week) oral carcinogenicity study of vinyl chloride in rats. Food Chem Toxicol 29:713-718.

Experimental design: Groups of Wistar rats (100/sex/group in controls and the two lowest exposure groups; 50/sex at the highest exposure level) were administered vinyl chloride in the daily diet at intended initial dietary concentrations of 0, 0.46, 4.6, or 46 ppm for 149 weeks. Due to rapid evaporative loss of vinyl chloride from the food, liquid vinyl chloride was mixed with polyvinyl chloride granules to produce a mixture in which vinyl chloride was effectively encapsulated in polyvinyl chloride granules (Feron et al. 1975). The study authors trained the rats to a feeding schedule of 4 hours/day prior to the initiation of exposure to vinyl chloride in the diet. The authors noted that food consumption per hour was fairly constant during the 4-hour feeding period. Loss of vinyl chloride from food during the first hour, the second hour, and the final 2 hours was calculated. Periodic food intake measurements were made for the first hour, the second hour, and the final 2 hours. Based on these measurements, the study authors calculated the average oral intake of the combined sexes during the daily 4-hour feeding periods to be 0, 0.018, 0.17, and 1.7 mg/kg/day for the 0-, 0.49-, 4.49-, and 44.1-ppm groups, respectively (see Table A-3). Measurements of vinyl chloride in the feces were made periodically at 1 hour prior to the feeding period, the end of the 4-hour feeding period, and 4 and 9 hours later. The study authors considered the vinyl chloride content in the feces to have remained encapsulated in the polyvinyl chloride granules and thus not to have been available for absorption from the gastrointestinal tract. The amount of vinyl chloride in the feces was subtracted from the calculated daily oral intake of vinyl chloride to arrive at what the study authors termed “actual oral exposure levels” of 0, 0.014, 0.13, and 1.3 mg/kg/day for the 0-, 0.49-, 4.49-, and 44.1-ppm groups, respectively (see Table A-3). Results of toxicokinetic assessments for vinyl chloride indicate that, following absorption, vinyl chloride and its metabolites are not excreted in appreciable amounts in the feces. Types and incidences of neoplastic and nonneoplastic liver lesions were determined at the end of the study.

Table A-3. Exposure Levels and Oral Intake Values for Rats Exposed to Vinyl Chloride in the Diet for 149 Weeks

Mean initial dietary level (ppm)	Oral intake (mg/kg/day)[a]	Adjusted oral intake (mg/kg/day)[b]	Estimated absorbed dose (mg/kg/day)[c]
0	0	0	0
0.49	0.022	0.018	0.014
4.49	0.21	0.17	0.13
44.1	2.1	1.7	1.3

[a]Assuming no loss of vinyl chloride by evaporation from the diet.
[b]Oral intake, adjusted for evaporative loss from the diet during the daily 4-hour feeding periods.
[c]Oral intake of vinyl chloride (adjusted for evaporative loss and the amount excreted in the feces, which was considered to have remained encapsulated in the polyvinyl chloride granules and not to have been available for absorption).

Source: Til et al. (1983, 1991)

Effects noted in study and corresponding doses: The critical nonneoplastic effect was determined to be liver cell polymorphism, which was classified by severity (slight, moderate, severe). The incidences of this lesion are listed in Table A-4.

Table A-4. Incidences of Male and Female Wistar Rats Exhibiting Slight, Moderate, or Severe Liver Cell Polymorphism Following Daily Oral Exposure to Vinyl Chloride in the Diet for 149 Weeks

	Oral intake (mg/kg/day)							
	Males				Females			
	0	0.018	0.17	1.7	0	0.018	0.17	1.7
Number of rats examined	99	99	99	49	98	100	96	49
Slight	27	23	26	19	46	41	49	23
Moderate	4	4	7	10[a]	14	13	8	15[b]
Severe	1	1	1	3	2	3	4	9[c]

[a]Significantly different from controls according to Fisher's exact test ($p<0.001$).
[b]Significantly different from controls according to Fisher's exact test ($p<0.05$).
[c]Significantly different from controls according to Fisher's exact test ($p<0.0001$).

Source: (Til et al. 1983, 1991)

A LOAEL of 1.7 mg/kg/day was identified for statistically significantly increased incidences of liver cell polymorphism in male and female rats. The NOAEL for nonneoplastic liver effects is 0.17 mg/kg/day. An increase in the incidence of female rats with many hepatic cysts was also observed at the highest dose (1.7 mg/kg/day). Other histopathologic lesions, described as hepatic foci of cellular alteration, were observed at all dose levels in female rats and in high-dose male rats, but were not used to derive an MRL because they are considered to be preneoplastic lesions. MRLs are protective only for non-neoplastic effects and do not reflect cancer risk.

The liver cell polymorphism incidences reported by Til et al. (1983, 1991) were also used as the basis of the RfD of 0.003 mg/kg/day for vinyl chloride derived by the U.S. EPA (EPA 2000). However, EPA

used the estimated absorbed dose of 0.13 mg/kg/day as the NOAEL, rather than the adjusted oral intake NOAEL of 0.17 mg/kg/day used by ATSDR. EPA (2000) applied the Clewell et al. (1995) PBPK model for vinyl chloride to the low-, mid-, and high-dose groups (estimated absorbed doses of 0.014, 0.13, and 1.3 mg/kg/day, respectively) to generate dose metrics of 0.3, 3, and 30 mg vinyl chloride metabolites/L liver, respectively. The EPA (2000) rationale for using the total amount of metabolite generated divided by the volume of liver tissue as the dose metric for liver toxicity included evidence that vinyl chloride-induced liver toxicity is related to the production of reactive intermediates and that binding to liver macromolecules correlates well with total metabolism (Watanabe et al. 1978). In EPA's derivation of the RfD, it was assumed that all of the metabolism of vinyl chloride occurred in the liver. EPA (2000) simulated a continuous human exposure scenario (ingestion of 1 ppm of vinyl chloride in water or 0.286 mg/kg/day, assuming consumption of 2 L water/day for a 70-kg person) using the Clewell et al. (1995) model, which resulted in a human internal dose metric of 1.01 mg metabolite/L liver. The ratio of the value for the human internal dose metric 1.01 mg metabolite/L liver) to the vinyl chloride intake of 0.286 mg/kg/day in the simulated human exposure scenario (1.01 ÷ 0.286 = 35.31) was used by EPA (2000) to convert from the rat dose metric (3 mg metabolite/L liver) at the NOAEL (0.13 mg/kg/day estimated absorbed dose) to a human equivalent dose (i.e., the rat NOAEL of 0.13 mg/kg/day divided by 35.31 equals a human equivalent dose of 0.09 mg/kg/day). EPA considered this approach to be adequate because vinyl chloride metabolism is linear in the dose range that includes the NOAEL of 0.13 mg/kg/day identified in the rat study of Til et al. (1983, 1991).

EPA (2000) assessed the feasibility of using Benchmark Dose Modeling on incidence data for liver cell polymorphism in the study of Til et al. (1983, 1991). Incidence data for moderate and severe grades of liver cell polymorphism were combined for both sexes and summed to produce one control group and three exposure groups (moderate + severe incidences of liver cell polymorphism divided by the number of treated male and female rats at each dose level; 21/197 controls, 21/199 low-dose, 20/196 mid-dose, and 37/98 high-dose rats). The resulting incidence data for each dose metric (0.3, 3, and 30 mg metabolite/L liver) were subjected to Benchmark Dose modeling in order to statistically identify a threshold response for vinyl chloride-induced effects. The resulting dose metric values are shown in Table A-5.

Table A-5. LED_{10} Values Generated from Various Models to Liver Cell Polymorphism Incidence Data from Oral Exposure of Male and Female Rats to Vinyl Chloride in the Diet for 149 Weeks in the Study of Til et al. 1991

Model	LED_{10} (mg/L liver)[a]	*p*-value
Weibull (power≥1)	24.0	0.88
Gammahit	21.4	0.88
Quantal quadratic	13.8	0.96
Logistic	12.9	0.47
Multistage	11.8	0.79
Probit	11.6	0.44
Quantal linear	6.5	0.46
NOAEL	3.00 (0.13 mg/kg/day)	
LOAEL	29.9 (1.3 mg/kg/day)	

[a]LED_{10} is the lower 95% confidence limit of a 10% change in numbers exhibiting polymorphism evaluated as either moderate or severe. The NOAEL and LOAEL are shown for comparison.

Source: EPA (2000)

EPA (2000) noted that although all models provided adequate fit to the data, the liver cell polymorphism appeared to be only a high-dose phenomenon, the LED_{10} values ranged from 6.5 to 24.01 mg/L liver

(nearly a 4-fold range), and all modeled LED_{10} values were higher than the NOAEL of the study. EPA (2000) argued that there was no biological reason to choose the results of one model over another and that the dose-response characteristics present additional uncertainty due to the large gaps between dose levels. For these reasons, EPA (2000) chose to use the internal dose metric of 3 mg/L liver, corresponding to the rat NOAEL, rather than a benchmark LED_{10} value, to derive the RfD for vinyl chloride. EPA (2000) applied an uncertainty factor of 30 (3 for extrapolating from animals to humans using a dosimetric adjustment and 10 for intrahuman variability) to the HED of 0.09 mg/kg/day.

Therefore, the RfD = 0.09 mg/kg/day ÷ 30 = 0.003 mg/kg/day. The chronic-duration oral MRL for vinyl chloride is based on the same critical effect as that used by EPA (2000) to derive the RfD for vinyl chloride (i.e., the NOAEL for liver cell polymorphism in the oral rat study of Til et al. 1983, 1991). However, the point of departure for the chronic-duration oral MRL was the NOAEL of 0.17 mg/kg/day (average ingested dose), rather than the estimated absorbed dose of 0.13 mg/kg/day used by EPA (2000), based on the assumption that all of the vinyl chloride that remained in the diet (after volatilization) was available for absorption.

In deriving the MRL, the rat NOAEL of 0.17 mg/kg/day was converted to a human equivalent dose using the PBPK models described in Clewell et al. (2001) and EPA (2000) to extrapolate from rats to humans. Source code and parameter values for running the rat and human models in Advance Continuous Simulation Language (ACSL) were transcribed from Appendix C of EPA (2000). Parameter values used in the interspecies extrapolation are presented in Table A-6. Accuracy of the implementation of the model in ACSL (v. 11.8.4) was checked against observations reported in Gehring et al. (1978), also reported in Clewell et al. (2001) (results shown in Figure A-2). The total amount of vinyl chloride metabolized in 24 hours per L of liver volume was the rat internal dose metric that was used in determining the human dose that would result in an equivalent human dose metric. One kilogram of liver was assumed to have an approximate volume of 1 L. Exposures in the Til et al. (1983, 1991) rat dietary study were simulated as 4-hour oral exposures, for which, the average daily dose was equivalent to the NOAEL dose for liver effects (ADD, 0.17 mg/kg/day). This dose was uniformly distributed over a 4-hour period (i.e., 0.0425 mg/kg/hour for 4 hours, followed by 16 hours at 0 mg/kg/hour). Dose metrics reflect the cumulative amount of vinyl chloride metabolized over the 24-hour period.

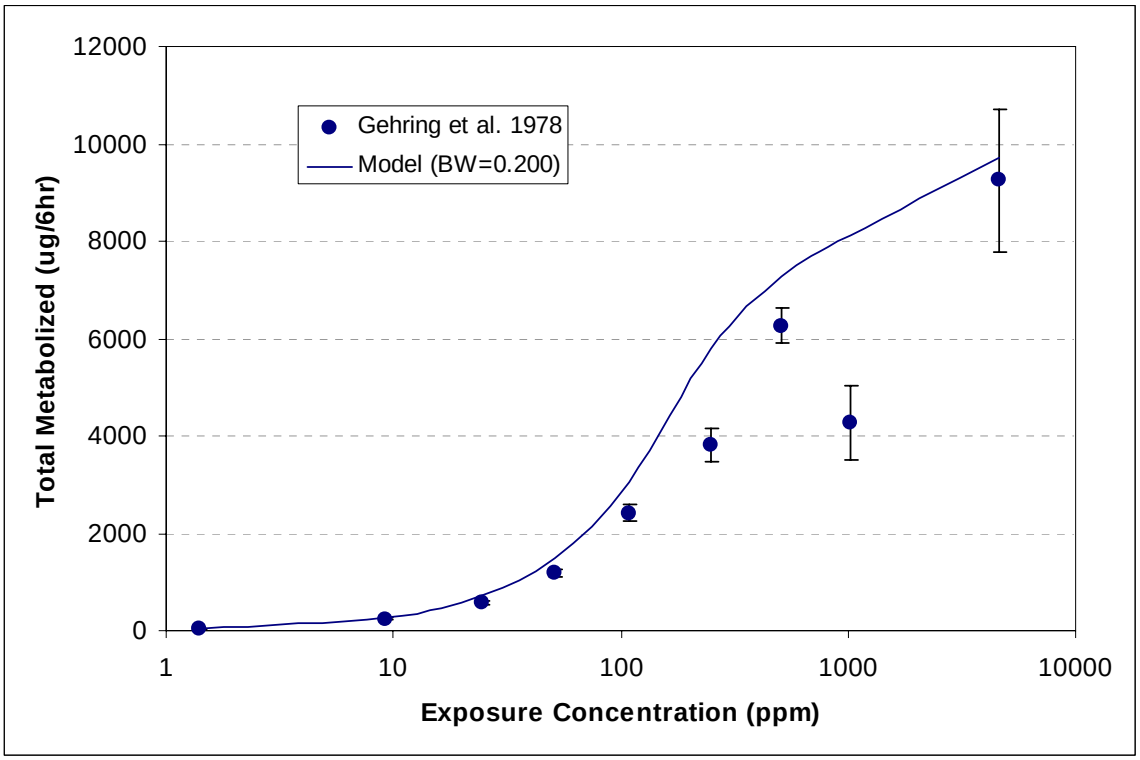
Table A-6. Parameter Values for Rat and Human Models

		Model	
Parameter	Definition	Rat	Human
BW	Body weight (kg)	0.377 (m) 0.204 (f)	70
VLC	Liver volume (fraction of body)	0.05	0.026
VFC	Fat volume (fraction of body)	0.12	0.19
VSC	Slowly-perfused tissue volume (fraction of body)	0.75	0.63
VRC	Rapidly-perfused tissue volume (fraction of body)	0.05	0.064
QCC	Cardiac output (L/hr-kg body weight)	18.0	16.5
QPC	Alveolar ventilation rate (L/hr-kg body weight)	21.0	24.0
QLC	Liver blood flow (fraction of cardiac output)	0.25	0.26
QFC	Fat blood flow (fraction of cardiac output)	0.09	0.05
QSC	Slowly-perfused blood flow (fraction of cardiac output)	0.15	0.19
QRC	Rapidly-perfused blood flow (fraction of cardiac output)	0.51	0.5
PB	Blood:air partition coefficient	2.4	1.16
PL	Liver:blood partition coefficient	0.7	1.45
PF	Fat:blood partition coefficient	10.0	20.7
PS	Slowly-perfused partition coefficient	4.0	0.83
PR	Rapidly-perfused partition coefficient	0.7	1.45

Table A-6. Parameter Values for Rat and Human Models

Parameter	Definition	Model	
		Rat	Human
VMAX1C	Maximum rate of oxidative metabolism (mg/hr-kg body weight)	4.0	4.0
VMAX2C	Maximum rate of oxidative metabolism (mg/hour-kg body weight)	2.0	0.1
KM1	Michaelis-Menten coefficient for oxidative metabolism (mg/L)	0.1	0.1
KM2	Michaelis-Menten coefficient for oxidative metabolism (mg/L)	10.0	10.0
KCO2C	Rate constant for formation of CO_2 from oxidative metabolite ($hour^{-1}$)	1.6	1.6
KGSMC	Rate constant for conjugation with GSH ($hour^{-1}$)	0.13	0.13
KFEEC	Rate constant for conjugation, not with GSH ($hour^{-1}$)	35.0	35.0
CGSZ	Initial GSH concentration in liver (µmol/L)	5,800	5,800
KBC	Rate constant for GSH catabolism ($hour^{-1}$)	0.12	0.12
KS	Coefficient controlling resynthesis of GSH (µmol/L)	2,000	2,000
KZC	Zero-order rate constant for resynthesis of GSH (µmol/hour)	28.5	28.5
Ka	Gastrointestinal absorption rate constant ($hour^{-1}$)	3.0	

Figure A-2. Predicted and Observed Relationship Between Air Exposure Concentration and Rate Metabolism of Vinyl Chloride in Rats*



*Measurements of metabolites (non-volatile ^{14}C in carcass) were made immediately following a 6-hour exposure to [^{14}C]vinyl chloride in air. Circles represent observations (± SD); the line shows the corresponding simulations.

The human model was run iteratively, varying the ADD, until the model converged with the internal dose estimate shown in row 1 in Table A-7 (rat, male). The value for the Km1 for oxidative metabolism in humans was assumed to be equal to the Km1 value for rats (0.1 mg/L) (EPA 2000). The human ADD was assumed to be uniformly distributed over a 24-hour period. The resulting HED was 0.09 mg/kg/day (see Table A-7). Additional simulations were performed assuming that the ADD was distributed over a 12-hour period (to simulate exposure from drinking water or food during the day only). The resulting dose metrics were very similar to the 24-hour estimates (data not shown).

Table A-7. Summary of Internal Dose Predictions and Corresponding Human and Rat Equivalent Doses

Species	BW (kg)	Km1 mg/L	ED (week)	EF1 (day/ week)	EF2 (hour/ day)	ADD (mg/kg/day)	DM (mg/L)
Wistar rat							
Male	0.377	0.1	149	7	4	0.17	3.16
Female	0.204	0.1	149	7	4	0.17	3.16
Human	70	0.1	3,640	7	24	0.09	3.16

ADD = average daily administered dose; BW = body weight; DM = dose metric equals the total amount of metabolite formed in 24 hours per L of liver; ED = exposure duration; EF = exposure frequency; Km1 = Michaelis-Menten constant for oxidative metabolism

ATSDR accepted the rationale used by EPA (2000) for not using Benchmark Dose modeling results for incidences of the critical effect (liver cell polymorphism in the oral rat study of Til et al. 1983, 1991) in the risk assessment. Therefore, the HED of 0.09 mg/kg/day, associated with the rat NOAEL of 0.17 mg/kg/day (Til et al. 1983, 1991), served as the basis for the chronic-duration oral MRL for vinyl chloride. A total uncertainty factor of 30 (3 for extrapolating from animals to humans using a dose metric conversion and 10 for human variability) was applied to the HED.

Therefore, the chronic-duration oral MRL = 0.09 mg/kg/day (HED) ÷ 30 = 0.003 mg/kg/day.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans using a dose metric conversion
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.
If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: N/A

Other additional studies or pertinent information which lend support to this MRL: This MRL is reinforced by a study by Feron et al. (1981) in which rats were fed diets containing PVC powder.

Increased areas of cellular alteration (consisting of clear foci, basophilic foci, and eosinophilic foci) were observed in the liver of rats at an oral intake of vinyl chloride monomer of 1.8 mg/kg/day.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 →

Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

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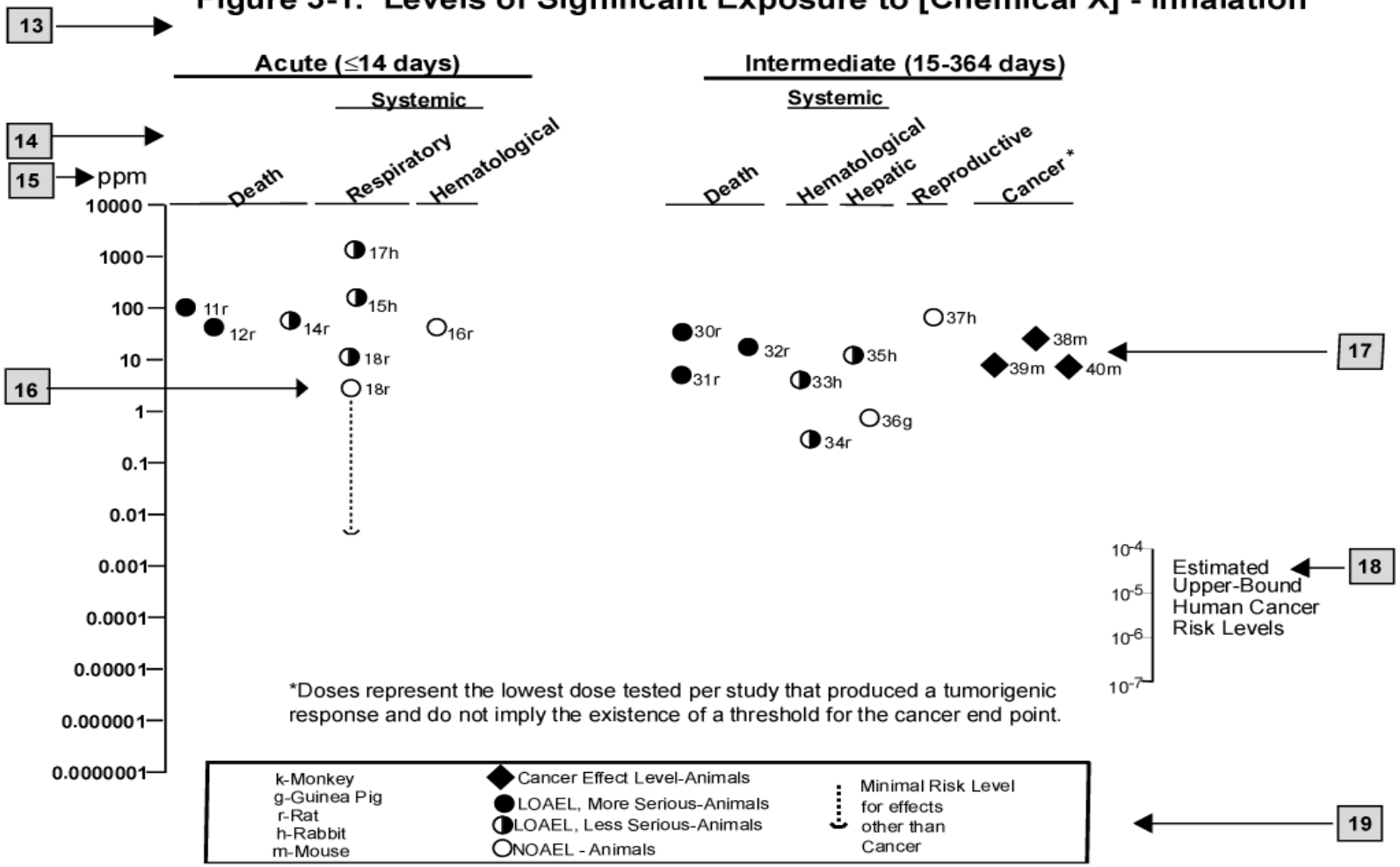
[a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D. INDEX